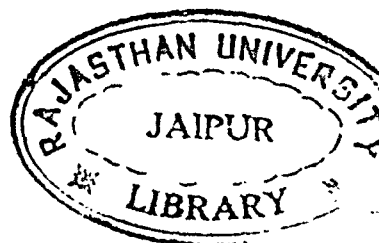


ACTA MEDICA SCANDINAVICA

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Supplementum CXXXVII, *Thor Sällström* (Stockholm): Das Vorkommen und die Verbreitung der multiplen Sklerose in Schweden.

Supplementum CXXXVIII, *Fritz Karlström* (Karlstad, Sweden): The Cl-ion content of the cerebrospinal fluid and its relation to the Cl-ion content of the blood.

Anémie à type pernicleux chez un enfant de 9 mois.

Par

JENS DEDICHEN, O.-lo.

L'auteur regrette beaucoup qu'une faute qui risque de fausser tout le tableau clinique s'est glissée dans le manuscrit au cours des corrections des épreuves de son article dans le fasc. I du vol. CXI. A la page 91, à l'alinéa «Examen de laboratoire» la Wall est marquée comme positive, alors qu'elle n'a jamais été que *négative* ce qui a pu être constaté à chaque nouvel examen. L'auteur espère que le fait qu'il n'y a aucune discussion de cette réaction positive, aura déjà fait soupçonner à ses collègues qu'il s'agit d'une faute d'impression (un -+ écrit à la machine interprété comme un plus), et présente toutes ses excuses pour son manque d'attention.

(From Försvarsväsendets kemiska anstalt, Research department, Head prof. G. Ljunggren, Ulriksdal, Sweden).

Note on the determination of carbon monoxide in blood.

By

BO NORBERG.

(Submitted for publication May 18, 1942).

For clinical and other objects a specific, rapid and sensitive method for the determination of carbon monoxide in blood is often needed. The method for detection of carbon monoxide newly described by Wolff (11) seemed promising for this purpose. A closer investigation, however, revealed certain limitations which will be shortly discussed below.

The principle of Wolff's method is to coagulate the oxyhemoglobin by means of heat under such conditions, that the carbon monoxide hemoglobin remains in solution and may be estimated after filtration.

Before testing Wolff's method, a suitable technic for the estimation of the carbon monoxide hemoglobin in the filtrate was sought for. In applications of Wolff's method, comparison photometry (3, 13) and absolute photometry (7) are used. The latter, being more accurate, was also adopted for this purpose. The Zeiss step photometer was used. As the specific extinction coefficients for oxyhemoglobin and carbon monoxide hemoglobin for the filtra of the apparatus could not be found in the literature, the said values were determined on five samples of human blood, whose oxygen capacity was determined by a standard method (9). Five to seven dilutions were made of each sample and cells giving extinction values of 0.5—1 were used in the photometry. The resulting mean values for the specific extinc-

tion coefficients, k , per mg/ml with the dispersion, $\sigma = \sqrt{\frac{\sum \Delta^2}{n-1}}$, and quotients $k_{\text{HbO}_2}/k_{\text{HbCO}}$, are given in table 1.

For control purposes the k values were calculated from the values of Newcomer (6) corrected for the spectral sensitivity of the human eye (12), the spectral intensity of the lamp (5, the temperature of the tungsten filament was assumed to be 3000°K), and the transmission of the filter (1)

$$\text{according to } k \approx \log \frac{I_1 + I_2 + \dots + I_n}{\frac{I_1}{10^{k_1}} + \frac{I_2}{10^{k_2}} + \dots + \frac{I_n}{10^{k_n}}}$$

Here k is the sought extinction coefficient, I_1, I_2, \dots, I_n are the relative intensities 80, 85, 90, 93, 96, 98 and 100 transmitted by the filter, and k_1, k_2, \dots, k_n the corrected specific extinction coefficients for the corresponding wave lengths. The two sets of values agree well, considering the approximations in the calculated values.

Table 1.

Specific extinction coefficients per mg/ml of oxyhemoglobin and carbon monoxid hemoglobin for filters of the Zeiss step photometer.

Filter	Experimental values			Calculated values		
	$k_{\text{HbO}_2} \pm \sigma$	$k_{\text{HbCO}} \pm \sigma$	$\frac{k_{\text{HbO}_2}}{k_{\text{HbCO}}}$	k_{HbO_2}	k_{HbCO}	$\frac{k_{\text{HbO}_2}}{k_{\text{HbCO}}}$
S. 57	0.700 ± 0.034	0.705 ± 0.025	0.99	0.695	0.714	0.97
S. 53	0.694 ± 0.031	0.763 ± 0.033	0.91	0.608	0.758	0.80
S. 50	0.419 ± 0.023	0.455 ± 0.026	0.92	0.344	0.394	0.87
S. 47	0.565 ± 0.022	0.530 ± 0.021	1.07	0.636	0.536	1.19
S. 43	2.06 ± 0.10	1.90 ± 0.17	1.09	1.71	1.28	1.34

To test Wolff's method blood samples were analysed by this method and at the same time by a standard gasometric method (8) and by the volumetric method of Wennesland (10). Blood samples were prepared from untreated blood and blood saturated with carbon monoxide (10 % by volume in air).

Technics used:

Estimation with Wolff's method: 0.2 ml of blood are hemolyzed in 0.8 ml of water and 4 ml of acetate buffer added. The buffer solution is prepared from 3 volumes of three times normal sodium acetate (408 g NaAc. $3 \text{ H}_2\text{O}$ + water to make 1 liter) and 1 volume of five times normal acetic acid. The pH should be

5.0—5.1. We checked it with the glass electrode. Of the blood-buffer mixture 0.5 ml are diluted with 3.5 ml of water and the extinction, E_{Hb} , measured with filter S. 57 and a 1 cm cell (total hemoglobin). The remainder of the blood-buffer solution is put in a water thermostat at 50.0° C for exactly *five* minutes and then cooled in water and filtered. Photometry on the filtrate in a 0.5 cm cell with the same filter (E_{HbCO} , CO hemoglobin) or S. 43, as one wishes. Calculation according to the absorption law (Lambert-Beer) gives $E_{\text{Hb}} \cdot 38 = \text{oxygen capacity in \% by volume}$, and $E_{\text{HbCO}} \cdot 9.5 = \text{\% by volume of CO}$ (for filter S. 43: $E_{\text{HbCO}} \cdot 3.4$).

Wenneslands method: the original technic was followed but for the bromination. To the sample is added 5 ml of a strong acetate buffer (35 g NaAc 3 H₂O + 100 g glacial acetic acid + 100 ml water, see Hurka, 2) are added. Without this buffer the results were often poor. Bromine vapours are blown through this solution, and the excess bromine boiled away. The use of phenol or formic acid to eliminate the excess of bromine does not give so good results as boiling. After addition of 5 ml of two times normal H₂SO₄, the final titration is done as described by Wennesland.

Results and discussion.

Some 25 samples were analysed with all three methods. The method of Wennesland agreed very well in most case with the standard method, whereas the values according to Wolff were always low. The mean recovery in the Wolff values was 82.5 % of the carbon monoxide hemoglobin with a practical margin of error of ± 29 %. Moreover, incomplete coagulation of the oxy-hemoglobin was demonstrated in special experiments (in contrast to Paul and Wretling, l. c.). This blank value corresponded on an average to 0.47 % CO by volume. Values of about 0.5 % CO by volume must therefore be checked by addition of sodium hyp-sulfite. Disappearance of the absorption bands in the green and yellow (or approximately twofold increase of the extinction in S. 43) indicates the absence of carbon monoxide in the filtrate. The variations in the blank values also make systematical correction for the blank useless. On the contrary, the carbon monoxide values must be multiplied by 100/82.5 to correct for the loss of carbon monoxide hemoglobin during the coagulation. In table 2 one series of

experiments is demonstrated together with the corrected Wolff values. The results are given as absolute values, which seems to be more reasonable than relative values, as has also been pointed out by Kallner (4).

Table 2.

Carbon monoxide estimations in blood by different methods. All values in % CO by volume.

Sample	Gasometric method	Titrimetric method	Photometric method (Wolff), corrected values		
			Filter S. 57	Filter S. 43	
1	11.18	11.12	10.7	10.3	
2	8.9	9.0	8.6	8.9	
3	6.74	6.90	6.3	6.8	
4	4.43	4.70	4.16	4.48	
5	2.30	2.50	2.52	2.58	
Sample	Photometric method (uncorrected values).				
	Filter S. 57	S. 50	S. 47	S. 53	S. 43
1	8.8	8.56	8.8	8.45	8.46
2	7.1	7.2	6.9	7.15	7.35
3	5.2	5.2	5.46	5.50	5.60
4	3.42	3.56	3.8	3.70	3.69
5	2.07	2.16	2.36	2.35	2.13

Every value is the mean of duplicate or triplicate analyses.

Summary.

The method for detection of carbon monoxide in blood of E. Wolff may also be used for the quantitative analysis of CO (3, 7, 13). The large error through varying coagulation of both oxyhemoglobin and carbon monoxide hemoglobin restricts its usefulness to cases where rapidity is of more value than precision.

Where precision is needed, the method of Wennesland is recommended.

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Aus der Medizinischen Klinik zu Lund, Schweden. (Chefarzt: Professor Dr. Sven Ingvar.)

Coarctatio aortae.

Von

Dozent Dr. ERIK ASK-UPMARK.

(Bei der Redaktion am 2. März 1942 eingegangen.)

Unter Coarctatio aortae versteht man eine gewöhnlich hochgradige Verengung der Lichtung des Aortenbogens, in der Regel unterhalb der Abzweigung der Art. subclavia sin., nahe der Insertion des Ligament. Botalli. Der Zustand, den man auch als Isthmusstenose bezeichnet hat, ist von grossem anatomischem, physiologischem und klinischem Interesse. Anatomisch steht die Frage nach dem formalgenetischen Entstehungsmechanismus seit langem im Vordergrund. Physiologisch sind die bei der Coarctatio aortae vorliegenden, eigentümlichen Blutdruckverhältnisse von ganz besonderem Interesse. Klinisch hat der Zustand, obwohl an sich selten, eine gewisse Bedeutung erlangt einmal als eine differentialdiagnostisch und prognostisch eigentümliche Gruppe unter den juvenilen Hypertonien, zum andern auch wegen seines nicht zum wenigsten in der forensischen Medizin beachteten Zusammenhanges mit plötzlichem Tode jüngerer, anscheinend gesunder Personen. Nachstehend gebe ich eine kurzgefasste Beschreibung dreier an der Lunder Medizinischen Klinik beobachteten Fälle von Coarctatio aortae und anschliessend eine kurze Analyse des Zustandes.

Material.

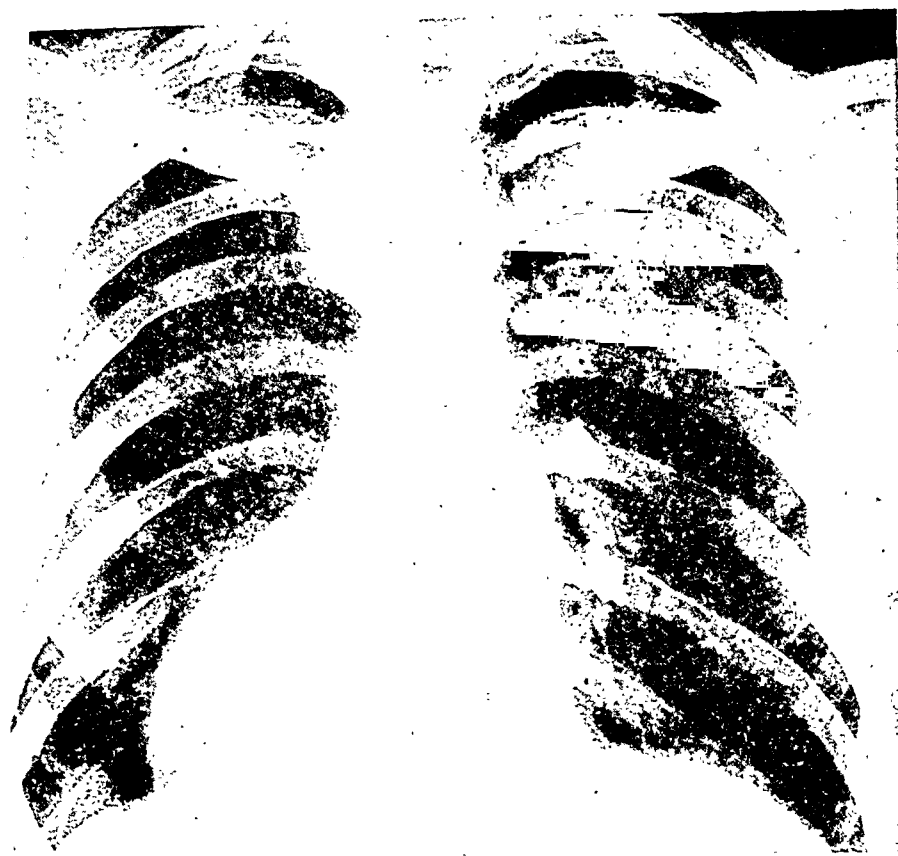
Fall 1. Mann, 32 Jahre, Gärtner. Med. Klin. 1506/1941.

Klinikaufnahme 23. 6. In der Klinik am 4. 9. gestorben.

Krankengeschichte: Die Eltern und zwei Brüder leben und sind gesund. Seit 5 Jahren verheiratet, Frau und ein Kind gesund. Regelmässige Mahlzeiten, viel Milch und Gemüse. Arbeitet als Gärtner. Militärische Dienstzeit als Ersatzreserve während 60 Tagen abgeleistet; doch wurde er soeben als kriegsverwendungsfähig eingemustert. Als Kind Morbilli, Scarlatina, sonst gesund; kein rheumatisches Fieber. — Der Mann erkrankte am 12. 6. 1941 mit Schüttelfrösten und Fieber. Die Temperatur hielt sich um 38°, doch hatte der Kranke sonst keine subjektiven Beschwerden, namentlich keine Gelenkschmerzen. Am 23. 6. kam er in die Klinik.

Status und klinischer Verlauf: Bei der Aufnahme in die Klinik war der Allgemeinzustand gut, Temperatur 37.5° C, Puls 84, Senkungsreaktion 22/51 nach 1 bzw. 2 Stunden, Blutdruck 210/90 (am linken Arm gemessen). Die Nägel der rechten Hand waren normal, die der linken leicht uhrglasförmig, namentlich am Daumen, der auch trommelschlegelförmig war. Ausgesprochene Pulsationen der Halsgefässe, sonst wurde leider nicht nach oberflächlichen Pulsationen gesucht. Kapillarpuls sichtbar (an der linken Hand). Kein Femoraliston. Augenfundi o. B. Die physikalische Untersuchung der Mundhöhle, Lungen, Bauchorgane und Reflexe erhob normale Befunde. Herz: Keine Pulsationen, kein Frémissement, kein palpabler Iktus. Rechte Grenze nicht seitlich des Sternalrandes, linke Grenze gleich medial von der Mamillarlinie. Im linken I 3—I 2 ein starkes systolisches Geräusch, systolische Unreinheit an der Spitze und ein schwächeres, systolisch pfeifendes Geräusch im rechten I 2, wo auch ein diastolisches Geräusch zu hören ist. — In der Klinik die ganze Zeit Fieber, im allgemeinen zwischen 38° C und 39° C. Mit der Zeit verschlimmerte sich der Allgemeinzustand zunehmend. Der Blutdruck schwankte ein wenig, war aber immer hoch (185/75, 175/75, 200/65), wenn er am linken Arm gemessen wurde; dagegen war der Blutdruck bei Messungen am rechten Arm deutlich gesenkt (festgestellte Werte: 85/70, 70/55, 90/70). Wiederholte Nachforschungen nach Hautembolien unter der Fusssohlensauscultation ad modum Ask-Upmark (1938) blieben ergebnislos. Trotz verschiedener Therapieformen (Immunotransfusionen, Heparin-Prontosil usw.) verschlimmerte sich der Zustand dauernd und Exitus trat am 4. 9. ein.

Laboratoriumsbefunde: Die Röntgenuntersuchung des Thorax (unter Leitung von Dozent Dr. Hellmer) am 26. 6. zeigte eine verstärkte Rundung der arteriellen Herzkammer, eine verlängerte und stärker gewundene Aorta thoracica, kleine, regelmässige, etwas beschleunigte Pulsationen; bei der Diaskopiekontrolle am 16. 7. war das Herz vergrössert, die Spitzenpartie stark gerundet, Verbreiterung nach rechts und starke Ausbuchtung nach rückwärts; am 22. 8. hatte sich das Herz wahrscheinlich weiterhin



1. Fall 1. Radiogram. Linksseitige Hypertrophie. Rippenusuren nur links.
Bild umgekehrt reproduziert.

grössert, die linke Herzgrenze befand sich kaum 2 Fingerbreit von der linken Thoraxwand und die Aorta wölbte sich links erheblich vor mit starken Pulsationen. Wiederholte Elektrokardiogramme (24. 6., 17. 7., 8) zeigten Linkstypus, negative T_{III} und schliesslich auf 0.24 verlängerte Überleitungszeit.

Blutmorphologische Befunde bei der Aufnahme: Hb 93%, rote Blutkörperchen 4.56 Millionen, weisse 6,900; Differentialzählung: Neutrophile 60%, Eosinophile 1%, Lymphocyten 19%, Monocyten 3%; das Blut verblieb in der Klinik relativ stationär (es ist zu bemerken, dass der Patient hier 11 Immunotransfusionen zu je 200—350 cm³ erhielt). Die Werte der Senkungsreaktion schwankten: bei der Klinikaufnahme 22/51 Wochen später 30/66, in den letzten 6 Wochen aber sanken sie ab auf 12/27, 8/18 und 5/11. Bei 4 Blutzüchtungen ergab sich positives Wachstum von *Streptococcus viridans*. Im Harn kein Zucker, Eiweiss oder Urobilinogen; das Sediment war bei wiederholten Bestimmungen in der Regel o. B., einmal wurden vereinzelte rote Blutkörperchen gefunden. Hämoglobinmengen zwischen 800 und 1,600 cm³, in der Regel etwa 1,000 cm³.

Autopsie am 5. 9. (Dozent Dr. Ahlström): Der Herzbeutel enthielt 100 cm³ klare Flüssigkeit. Das Herz (Gewicht 750 g) zeigt eine starke



Fig. 2. Fall 1. Linksseitige Rippenusuren. Bild umgekehrt reproduziert.

Hypertrophie der linken Kammer (Wanddicke 2.5 cm, hypertrophische Papillarmuskeln). In der rechten Herzhälfte normale Klappen, keine Thromben oder Embolien; das Foramen ovale ist für eine einige mm starke Sonde durchgängig; kein Septumdefekt. Mitralklappen o. B., abgesehen von einem zweipfenniggrossen Gebiet basal an der vorderen Mitralklappe, wo sich eine verruköse Veränderung mit beginnendem zentralen Zerfall findet; dieser zerfallende Stelle entsprechend ist das Endokard im linken Vorhof an einer pfenniggrossen Stelle etwas uneben mit matter Fläche. Keine Thromben im linken Vorhof. Die Aorta hat nur zwei Semilunarklappen; der Einschlagrand der vorderen Klappe ist ein wenig wulstig, und basal sieht man eine beginnende Lipoidablagerung, der Einschlagrand der hinteren Klappe ist an seinem linken Umfang wulstig, am rechten Umfang dünn und glatt, doch findet sich hier basal eine fibröse Verdickung; in der Mitte zeigt diese hintere Semilunarklappe ein erbsengrosses Aneurysma, das in die Kammer vorbuchtet und in seiner ganzen Ausdehnung perforiert ist. In den Kranzarterien keine Ostiumstenose oder Thrombosen, doch langgestreckte Lipoid-einlagerungen in der Wandung, besonders im linken absteigenden Ast. Keine Zeichen von Infarkten oder Narben an

der Herzmuskulatur. Die Aorta ascendens geht in normaler Weise von der linken Kammer ab und hat einen Umfang von 7—8 cm. Die Art anonyma fehlt als solche, und als erster Zweig geht vom Aortenbogen die Art. carotis communis dxt. mit einem Umfang von 35 mm ab. Etwa 1 cm links davon geht die Art. carotis communis sin. mit einem Gefäßumfang von 30 mm ab. Zwischen der Abzweigung dieser Arterie und der Art. subclavia sin. weist die Aorta an der Konvexität ein querlaufendes, mässig ausbuchtendes Aneurysma mit dünner Wandung auf. Gleich unter-

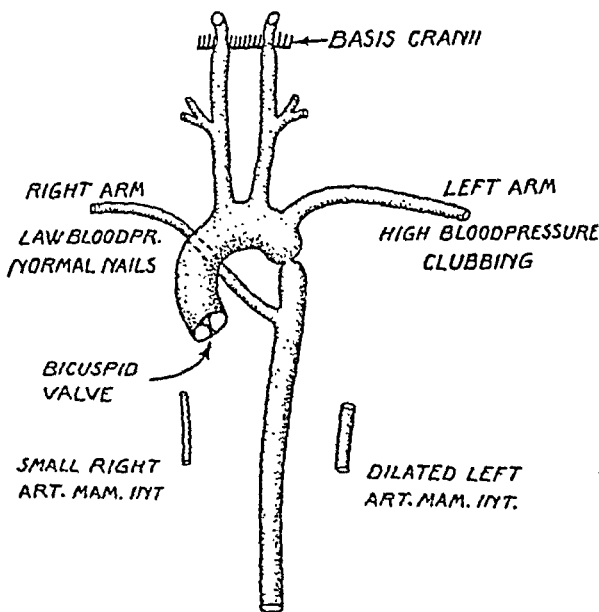


Fig. 3. Fall 1. Diagram über die anatomischen Verhältnisse.

halb der Abzweigung der Art. subclavia sin. verjüngt sich die Aorta recht plötzlich mit einer Verengung an der Stelle des Ansatzes des (völlig obliterierten) Lig. Botalli; die Aorta hat hier einen äusseren Durchmesser von 8 mm, während die innere Lichtung nur für eine 2 mm starke Sonde durchlässig ist. Gleich kaudalwärts von dieser Verengung erweitert sich die Aorta descendens und gibt die Art. subclavia dxt. ab, die hier einen Gefäßumfang von 30 mm hat und dann hinter und rechts vom Oesophagus auf ihrem Wege zum rechten Arm verläuft. Die Aorta ascendens zeigt eine beginnende Lipoideinlagerung in der Wandung, die gleich oberhalb der Verengung besonders markant ist und die auch in der linken Subclavia sowie in beiden Karotiden festgestellt wird, besonders ausgeprägt an der Carotisbifurkation, während unterhalb der Aortenverengung nur eine geringfügige Lipoideinlagerung und in der rechten Subclavia überhaupt keine solche festzustellen ist. Die linke Art. mammaria int. ist stark erweitert (Umfang 20 mm gegenüber 8 mm rechts), und ebenso sind die linken Interkostalarterien im Vergleich zu den rechten erheblich dilatiert. Die Karotiden werden in ihrer ganzen Länge freigelegt; bis hinauf zur Schädelbasis sind ihre Lichtungen deutlich erweitert, dann haben sie

normales Kaliber. An den basalen Hirngefässen sind keine Aneurysmata festzustellen; doch findet sich eine Anastomose zwischen der Art. basilaris und der linken Art. carotis interna. Im Gehirn sieht man links in den basalen Ganglien kleinere erweichte Partien, die von einer mit roten Zone umgeben sind. — Im übrigen sind Brust- und Bauchorganen im wesentlichen normal, doch findet sich fibrinuntermischte trübe Flüssigkeit sowohl in den Pleurahöhlen als der Peritonealkavität, ferner ist die Milz vergrössert (400 g), von schlaffer Konsistenz und mit schmieriger Schnittfläche, schliesslich zeigt die eine Niere einen pfenniggrossen, weissen Infarkt. Keine Thromben in den Beckenvenen oder in den Femoralisvenen gleich unterhalb des Lig. inguinale; doch war der rechte Unterschenkel geschwollen, so dass die Knöchelumrisse verschwommen waren.

Zusammenfassung: Ein bisher im wesentlichen gesunder 32-jähriger Mann erkrankt an Endocarditis lenta, zeigt eine eigentümliche Diskrepanz zwischen dem Blutdruck im rechten Arm, der niedrig ist, und dem im linken Arm gemessenen, der hoch ist, und stirbt nach 3 Monaten. Bei der Sektion findet man, dass sich die Viridansendocarditis auf dem Boden eines Missbildungskomplexes entwickelt hat, der sich im wesentlichen kennzeichnet durch Coarctatio aortae, zwei Aortenklappen statt drei, Abgang der rechten Art. subclavia von der Aorta unterhalb des stenosierten Teiles. Oberhalb des Hindernisses Atheromatose, teilweise hochgradig, unterhalb des Hindernisses keine.

Fall 2. Mann, 18 Jahre, Bauernsohn. Med. Klin. 2628/1941.

Am 13. 11. in die Klinik aufgenommen, wo er am 21. 11. starb.

Krankengeschichte: Vater 53 Jahre, gesund; Mutter 43 Jahre, gesund. Der junge Mann ist das vierte von 6 Kindern. Ein Bruder starb mit 3 Tagen an »Lungenentzündung«, ein zweiter mit $\frac{1}{2}$ Jahr ebenfalls an »Lungenentzündung«. Die übrigen Geschwister sind gesund, doch soll eine Schwester im Sommer 1940 Erythema nodosum gehabt haben. Als Kind Morbilli und Parotitis, sonst gesund, kein rheumatisches Fieber. Laut Angabe des Vaters konnte man an dem Patienten bereits als Kind starke Pulsationen in der Herzgegend beobachten, zum Unterschied von den übrigen Geschwistern. Guter Schüler, jetzt in der Landwirtschaft des Vaters tätig. — Im Februar 1939 Trauma gegen die linke Hüfte mit Epiphysenablösung, weshalb er 10 Wochen in einem anderen Krankenhaus zubringen musste. Während des damaligen Krankenhausaufenthaltes war der Puls zwischen 80 und 100 bei durchaus normaler Temperatur, der Blutdruck war 220/95, 220/85, 230/85, zudem stellte man eine starke Linksvergrösserung des Herzens fest, mit hebendem, breitem Iktus, systolischem und diastolischem Geräusch über der Aorta, Kapillarpuls und Palmarknips; man nahm eine Aorteninsuffizienz an. Der Patient hatte



Fig. 4. Fall 2. Radiogram, am 7/3 1941 aufgenommen (Bild umgekehrt reproduziert). Die Herzgewicht bei der Autopsie etwa 8 Monate später war nicht weniger als 1,400 Gram!

keine Herzbeschwerden, er konnte treppensteigen und mit dem Rade starke Steigungen nehmen, ohne sehr ausser Atem zu kommen.

Im September 1940 setzten katarrhale Beschwerden seitens der Luftwege ein (dickflüssiger, gelber Auswurf usw.), zudem plagte ihn eine zunehmende Müdigkeit und Mattigkeit, und bei Anstrengungen kam er leicht ausser Atem. Er konnte jetzt nur leichte Arbeiten verrichten und musste jetzt auch einmal jede Nacht Wasser lassen, was er früher nicht gebraucht hatte. Ende Oktober 1940 traten nächtliche Anfälle von Atemnot hinzu, so dass er aufrecht im Bett sitzen musste, ohne Schlaf finden zu können. Am 10. 1. 1941 kam er ins Krankenhaus und blieb hier 6 Wochen. Bei der Aufnahme bot er das Bild eines Schwerkranken, mit Blässe, kaltem Schweiß, starker Dyspnoe, Puls 130, Temperatur 38.9°, Blutdruck 160/50. Herz: starke Voussure, rechte Grenze 2—3 Fingerbreit lateral vom Sternalrand, linke Grenze in der vorderen Axillarlinie, einsetzende Spitzentöne, akzentuierter zweiter Aortenton. Die Röntgenaufnahmen am 10. 2. und 7. 3. zeigten eine Transversalbreite des Herzens von 19. 5 cm, davon 11 cm links von der Mittellinie bei einer Thoraxbreite von 30 cm; von 30 cm; ferner wurden gewisse Veränderungen in den Lungenfeldern festgestellt, die bei der zweiten Untersuchung wesentlich zurückgegangen waren. Das Ekg. am 26. 2. zeigte einen Sinusrhythmus von 135 und

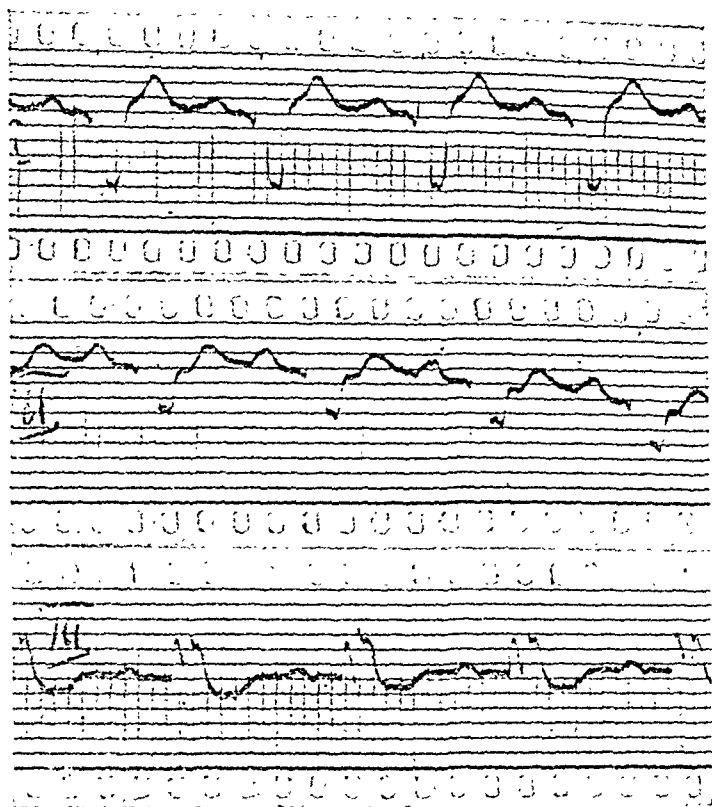


Fig. 5. Fall 2. Elektrokardiogram 9 Monate vor dem Tode. P und PQ normal, sonst bedeutende Veränderungen des Ventrikelkomplexes.

diphasische, verbreiterte Kammerkomplexe wie beim Schenkelblock. Der Patient wurde am 18. 3. ohne Dekompensationserscheinungen mit Digitalis entlassen. Er schonte sich dann zu Hause und fühlte sich wohl, bis Ende August stärkere Kurzatmigkeit und Müdigkeit wiederkehrten, ebenso die nächtlichen Anfälle von Dyspnoe. Die letzten 3 Tage vor der erneuten Klinikaufnahme waren die Beine angeschwollen. Am Tage der Aufnahme ein Anfall von Schwindel, wobei es ihm schwarz vor den Augen wurde.

Status und klinischer Verlauf: Bei der Aufnahme am 13. 11. und ebenso während des Verlaufs bietet der Patient das Bild eines Schwerkranken mit starker Dyspnoe in Ruhe, starker Zyanose der Lippen und Wangen, Ödeme an beiden Unterschenkeln. Keine Trommelschlägelfinger oder Uhrglasnägel. Temperatur 37.8°, Puls 115, Senkungsreaktion 79/110 in 1 bzw. 10 Stunden, Blutdruck 220/75. Der Blutdruck war am 17. 11. linker Arm 205/70, rechter Arm 190/70, linkes Bein 115/70, rechtes Bein 110/85; die entsprechenden Werte am 19. 11.: 205/65, 210/70, 110/70, 110/75. Medial von der rechten Skapula palpiert man subkutan eine pulsierende Arterie von Gänsefederweite. Herz: gewaltsame Pulsationen in einem bombierenden Praecordium. Breiter, hebender Iktus. Linke Herzgrenze nahe der Axillarlinie, rechte Grenze mehr als 2 Fingerbreite lateral

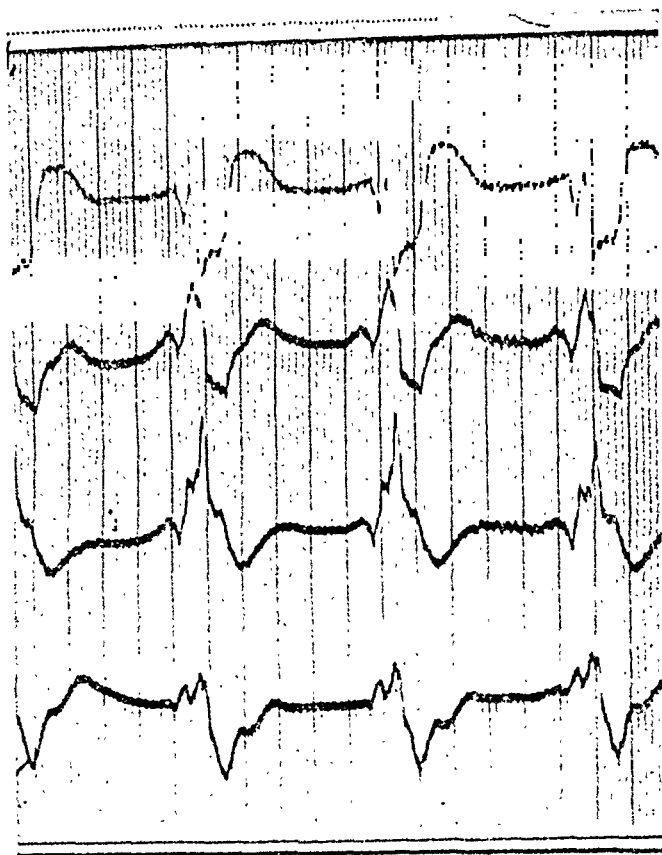


Fig. 6. Fall 2. Elektrokardiogram wenige Tage vor dem Tode. Man soll sich die scheinbare Ähnlichkeit mit dem sog. WPW-syndrom bemerken.

vom Sternalrande. Systolisches Geräusch, basal am stärksten. Kein Femoralistön. Im übrigen erlaubte der Zustand des Patienten keine eingehendere Untersuchung: gleichwohl wurde Lungenrasseln festgestellt, die Leber reichte bis in Nabelhöhe und die Reflexe waren normal. Der Venendruck wurde am 20. 11. mit 16.5 cm H₂O gemessen. Der Kranke war wenigstens anfangs bei vollem Bewusstsein, doch fiel ihm wegen der starken Dyspnoe das Sprechen schwer. Er wurde mit Strophantin intravenös sowie mit Sauerstoff und Sedativa behandelt, doch verschlimmerte sich der Zustand unaufhaltsam und am 21. 11. trat der Tod ein.

Laboratoriumsbefunde: Eine regelrechte Röntgenuntersuchung konnte mit Rücksicht auf den elenden Zustand des Kranken nicht ausgeführt werden, doch zeigte eine kursive Durchleuchtung ein sehr grosses, kräftig pulsierendes Herz. Das Elektrokardiogramm zeigte eine auf 0.11 abgekürzte Überleitungszeit sowie Verzweigungsblock vom Rechtstypus, also ähnlich wie bei dem sog. WPW-Syndrom. Blut: bei der Aufnahme Hb 75 %, rote Blutkörperchen 4.4 Millionen, weisse 22,800, Differentialzählung: Neutrophile 86 %, Monocyten 8 %, Lymphocyten 6 %. Die Harnmengen wechselten zwischen 600 und 1,000 cm³, das spezifische Gewicht zwischen 1,020 und 1,026; Albuminurie etwa 1 %₁₀₀.

Autopsie 22. 11. (Ahlström). Bombierung der Herzgegend. Ödeme an beiden Unterschenkeln. Stark erweiterte Art. mammar. int. Die rechte Lunge ist der Sitz einer ausgedehnten, teilweise gelatinös pneumonischen, teilweise kavernösen Tuberkulose mit Flüssigkeit in der rechten Pleura. Thyreoidea makroskopisch normal. Bauchorgane o. B., also keine Leber- oder Milzvergrößerung; Nieren und Nierenarterien waren makroskopisch normal, ebenso die Abzweigung der letzteren von der Aorta. Keine Thromben in den Becken- oder Femoralisvenen. Hirnsubstanz intakt, keine Blutungen in den basalen Ganglien oder im Hirnstamm (auch nicht in der Oblongata). Hirngefässe unverändert, ohne Zeichen von Arteriosklerose, Aneurysmata oder anderen Gefässmissbildungen. Im Herzbeutel eine etwas vermehrte Menge klarer Flüssigkeit; keine Zeichen einer Tbc-Perikarditis. Das Herz zeigt eine äusserst starke Linksvergrößerung und eine mässigere Rechtsvergrößerung, Gewicht 1,400 g. Keine Pulmonalistenosen. Die durchweg ein wenig verdickten Klappen zeigen keinerlei Spuren einer älteren oder frischen Endokarditis, auch keinerlei Andeutungen von Missbildungen (so hat die Aorta drei Klappen). Die linke Kammerwandung ist 22 mm dick, die rechte 7 mm. Das Septum ventriculorum buchtet stark in die rechte Kammerlichtung hinein. In der linken Kammer ein starkes Trabekelgeflecht und dicke Papillarmuskeln. Vom Aortenbogen gehen die grossen Gefässe in normaler Weise ab. Die Aorta zeigt hier keine arteriosklerotischen Veränderungen; man sieht nur einige kleinere, streifenförmige, gelbweisse Einlagerungen. Kein Aortenaneurysma. Die Aorta ascendens hat einen inneren Durchmesser von 6 cm, die Aorta descendens einen solchen von 5.5 cm. Die Art. carotis communis et int. werden bis an die Schädelbasis freigelegt; keine Aneurysmata. Zwei Zentimeter distal von der Abzweigung der Art. subclav. sin., die nicht abgeschnürt ist, verengt sich die Aorta descendens recht plötzlich und ist nur für eine Sonde von 3 mm Durchmesser durchlässig. An dieser Einschnürung inseriert das Lig. arter. Botalli, das kein Lumen hat. Die mikroskopische Untersuchung von Gewebe (Muskulatur) aus sowohl oberhalb als unterhalb des Hindernisses gelegenen Stellen des Körpers erhob völlig normale histologische Befunde an gröberen wie feineren Gefässen, gleichermassen in Armen und Beinen.

Zusammenfassung: 18-jähriger Mann, früher im wesentlichen gesund, seit 1 Jahr im Anschluss an die Entwicklung einer Lungentuberkulose Herzbeschwerden vom Typus der Herzdekompensation. Hoher Blutdruck an den Armen, niedriger Blutdruck an den Beinen, interskapular palpable Hautarterien, sehr starke Hypertrophie des Herzens, gewisse Ekg-Veränderungen. Sektion: Gewicht des Herzens 1,400 g, ausgesprochene Coarctatio aortae, Erweiterung der Artt. mammar. int., rechtsseitige Lungentuberkulose.

Fall 3. Mann, 69 Jahre, Arbeiter. Med. Klin. 781/1942.

Während des Lesens des Korrekturs in die Klinik aufgenommen, wo er nach zwei Tagen starb. Seit mehreren Jahren Herzbeschwerden, seit 3 Tagen Herzschmerzen und blutiger Auswurf. Blutdruck 220/110, Cheyne-Stokes Atmung, sehr schlechter Zustand, Exitus. Autopsie: Coarctatio aortae mit vollständiger Stenose von Isthmus aortae, Kollateralversorgung durch Aa.mam.int., ausgesprochener linksseitiger Herzhypertrophie, Stenose und Insuffizienz der Aortenklappen, mässiger Arteriosklerose der grösseren Arterien oberhalb des Hindernisses.

Geschichtliches.

Den ersten uns bekannten Fall von Coarctatio aortae beschreibt Morgagni 1760 in *De sedibus et causis morborum*. Er betraf eine Frau, bei der die Kliniker bemerkenswerterweise den Verdacht geäussert hatten, sie leide an einer »Geschwulst der Aorta«. Am Hôtel Dieu in Paris wurde dann im Jahre 1791 von dem damaligen Prosektor Paris ein ähnlicher Befund erhoben: bei der Sektion einer 50-jährigen Frau mit unbekannter Krankheitsgeschichte fand er am absteigenden Ast des Aortenbogens eine Verengung von Gänsefederweite; oberhalb dieser Stelle war die Aorta erweitert, unterhalb von normalem Kaliber. Dieser Fall wird oft als der erste beobachtete Fall von Coarctatio genannt, doch gebührt die Priorität dem grossen Alten in Padua. Der eigenartige anatomische Charakter des Zustandes einerseits, der oft dramatische Verlauf, nicht selten mit plötzlichem, unerwartetem Tode eines bis dahin als gesund angesehenen jungen Menschen andererseits dürften in der Folgezeit die Veröffentlichung einer beträchtlichen Anzahl dieser Fälle veranlasst haben. So konnte Wadstein im Jahre 1897 103 anatomisch gesicherte Fälle, darunter einen aus der Lunder Med. Klinik (damaliger Chefarzt Ribbing), zusammenstellen. Abbott veröffentlichte im Jahre 1928 eine oft zitierte Übersicht über 200 bis dahin beobachtete Fälle, Benkwitz und Hunter fügten im Jahre 1937 dieser Übersicht noch 75 später beobachtete Fälle hinzu, und auch in den allerletzten Jahren sind von verschiedener Seite einschlägige Befunde veröffentlicht worden; so verzeichnet der Index Medicus seit Benkwitz und Hunters Zusammenstellung etwa 80 Arbeiten über dieses Thema. In Schweden sind die Coarctatio aortae und damit zusammenhängende Fragestellungen von folgenden Autoren abgehandelt worden: Kjellberg

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(1859), v. Hofsten (1886), Wadstein (1897), Edgren (1897), Josefsson (1903), Köster und Forselius (1915), Ask-Upmark (1935), Wolke (1937); in Dänemark von Bartels (1912), Jacobsen (1935), Eskelund (1936), Söndergaard (1936), Nielsen (1940); in Finland von Wasastjerna (1903) und Klemola (1939); in Norwegen von Hansteen (1915) und Lutzow-Holm (1925). Der erste in vivo diagnostizierte Fall wird Oppolzer (1848) zugeschrieben; schon vorher hatte indessen Legrand (1835) in einem Falle von Coarctatio das Vorhandensein eines Hindernisses an der Aorta thoracica vermutet. Nach Abbot war bis zum Jahre 1928 die anatomisch bestätigte Diagnose Coarctatio aortae in 21 Fällen zu Lebzeiten der Patienten gestellt worden, eine Anzahl, die sich inzwischen nicht unwesentlich erhöht haben dürfte, seitdem das eigenartige klinische und röntgenologische Zustandsbild dieser Krankheit bekannter geworden ist.

Vorkommen.

Die Coarctatio aortae ist ein seltener Zustand. Wie Abbott angibt, wurde der Befund unter 5,000 Autopsien am Mass. General Hospital in 2 Fällen erhoben. Blackford verzeichnete in einer Zusammenstellung des Sektionsgutes von 6 Autoren unter insgesamt 68,300 Autopsien 44 Fälle, Andreesen aus Hamburger Krankenhäusern in den Jahren 1901—1927 unter 17,000 Autopsien 4 Fälle (bei Erwachsenen). Aus Lund ist bisher ein Fall beschrieben (von Wadstein, 1897); späterhin scheint kein Fall festgestellt worden zu sein (ausser den beiden jetzt hier beschriebenen), und dies bei einer jährlichen Anzahl von Obduktionen, die im letzten Jahrzehnt eher über als unter 500 Autopsien betragen hat. An der Lunder Medizinischen Klinik ist man seit fast zehn Jahren auf die Möglichkeit der Coarctatio aortae eingestellt; trotz einer jährlichen Patientenzahl von über 3,000 hat die Diagnose erst jetzt bei uns bestätigt werden können. Der Zustand muss also selten sein; andererseits überrascht es, dass so zahlreiche Autoren mehr als einen Fall beschrieben haben; so hat King (1937) 12 Fälle, Benkwitz und Hunter (1937) geben an, ausser dem von ihnen veröffentlichten noch etliche weitere Fälle gesehen zu haben, Stewart und Bailey (1941) beschreiben 14 Fälle usw. Um diese Fälle nicht zu übersehen, wird man sicherlich bei Juveniler Hyper-

tonie auch die Möglichkeit einer Coarctatio aortae ins Auge fassen und die klinische, röntgenologische und anatomische Analyse darauf abstellen müssen.

Coarctatio aortae ist bei Männern 3mal so häufig wie bei Frauen (Abbott). Menschen mit diesem Zustand werden in der Regel nicht sehr alt — etwa die Hälfte aller soll zwischen dem 20. und 40. Lebensjahr sterben, mindestens 25% sterben vor dem 20. Lebensjahr, und nur 10 % sollen 50 Jahre und älter werden. Diese hohe Sterblichkeit dürfte wenigstens zu einem Teil durch eine rechtzeitig gestellte Diagnose und dementsprechende Lebensweise gesenkt werden können, was um so erstrebenswerter ist, als im einschlägigen Schrifttum wiederholt hervorgehoben wird, dass es sich bei diesen Fällen oft um Plusvarianten in Hinsicht auf mentale und muskuläre Leistungen handelt. Dass der Zustand an sich keineswegs mit hohem Alter unvereinbar ist, steht ausser Frage. Reynaud beschrieb 1829 einen 92-jährigen Schuhmacher mit Coarctatio als Nebebefund bei der Sektion; wiederholt sind Fälle beschrieben worden, wo Personen mit Coarctatio aortae die Strapazen von Feldzügen und Revolutionen überstanden, ja, gar als Kampfflieger gedient haben (im vorigen Weltkrieg, Hart: 1920); unter den weiblichen Fällen finden sich verschiedene Multipara [Langmeads Fall 14 Kinder (1912), Weber und Price 11 Kinder (1912), Fawcett 9 Kinder, bei der Geburt des letzten gestorben (1905), Deckner 9 Kinder (1929), Haberer 7 Kinder (1923) usw.].

Pathologische Anatomie.

Man unterscheidet im Schrifttum zwischen zwei verschiedenen Formen von Coarctatio aortae: dem infantilen Typus, der sich kennzeichnet durch eine allgemeinere Verengung der Aorta zwischen der Abzweigung der Art. subclavia sin. und der Insertion des Lig. Botalli (sog. Isthmus aortae), und dem vornehmlich bei grösseren Kindern und bei Erwachsenen begegnenden Typus, gekennzeichnet durch eine abruptere Verengung der Aortenlichtung, als wäre eine Schlinge um das Gefäss gelegt und zugezogen worden; diese diaphragmaähnliche Verengung, die in der Regel hochgradig ist und nicht selten eine völlige Atresie der Lichtung bewirkt, liegt (meistens) an oder (bisweilen) gleich unterhalb der

Insertion des Lig. Botalli, zuweilen aber auch oberhalb dieses Punktes (in vereinzelt Fällen sogar oberhalb der Abzweigung der Art. subclavia sin.). Es gibt Fälle, wo bei einem und demselben Individuum sowohl der infantile als der »erwachsene« Typus vorgefunden werden, und es dürfte überhaupt zweifelhaft sein, ob man das Recht hat, scharf zwischen diesen beiden Formen zu unterscheiden, trotz ihres makroskopisch unterschiedlichen Aussehens: der »erwachsene« Typus begegnet man auch bei Kindern, und wenn der infantile Typus seltener bei Erwachsenen festgestellt worden ist, so dürfte dies daran liegen, dass er so oft mit anderen gröberen Anomalien (Septumdefekten, Pulmonalisatresie usw.) kombiniert ist, die schon frühzeitig den Tod herbeiführen. Mit dieser Einschränkung ist in der vorliegenden Arbeit in der Regel die Coarctatio von dem bei älteren (Abbott setzt die Grenze mit 2 Jahren an) Menschen gewöhnlich begegnenden Typus gemeint. Auch dieser Typus ist sehr häufig mit anderen Anomalien verbunden, von denen namentlich drei von Interesse zu sein scheinen.

1. Zwei Aortenklappen statt drei ist ein in über 25 % sämtlicher Fälle und in 50 % der Fälle mit Zerreißung der Aorta erhobener Befund.

2. Eine Veränderung der Aortenwand als solcher scheint nicht selten festgestellt zu werden. Man hat geltend gemacht, dass eine Hypoplasie der Aorta in 10 % der Fälle vorliege (Abbott), dass eine Mesoarthritis dissecans mit Degeneration und Aufsplitterung der elastischen Lamellen stattfinden könne (Babes und Mironescu 1910, Harrison 1939), sowie dass die Aorta ascendens nicht selten eine pergamentdünne Wand habe, die zwar oft durch den Druck gespannt sei, deren Dünne aber gewissermassen auch der Ausdruck einer präformierten Mediaschwäche sei.

3. Nicht selten liegt ein abnormer Ursprung der vom Aortenbogen ausgehenden Arterien vor. Von ganz besonderem Interesse erscheint die in meinem Fall (1) beobachtete Variante: Ursprung der rechten Subklavia unterhalb des Aortenhindernisses, ein auch früher bereits wiederholt erhobener Befund (ältere Fälle siehe Abbott, 1928, neuere u. a. Blackford's Fall 12, Love und Holm u. a.); hierauf wird noch zurückzukommen sein.

Der Coarctatiozustand hat sekundär zwei charakteristische Veränderungen im Gefolge: Herzvergrößerung und Entwicklung eines Kollateralsystems für die Blutversorgung der unteren Kör-

perhälfte. Die Aorta ascendens ist in der Mehrzahl der Fälle erweitert, doch nicht in allen (vgl. oben).

1. Die Herzveränderung besteht in einer Hypertrophie und Dilatation der linken Herzhälfte, in erster Linie natürlich der Kammer. Dass diese Vergrösserung ausserordentliche Masse annehmen und, obwohl in geringerem Grade, auch die venöse Herzhälfte einbeziehen kann, zeigt u. a. der eine meiner Fälle: das Herz des 18-jährigen jungen Mannes wog 1,400 g. Andererseits sei bemerkt, dass Fälle vorliegen, wo das Herz offenbar normal gross oder annähernd normal gross war. Hamilton und Abbott haben zehn derartige Fälle aus dem Schrifttum zusammengestellt; sehr bemerkenswert, obgleich bisher nicht hervorgehoben, erscheint mir der Umstand, dass es sich in der Mehrzahl dieser Fälle um Frauen handelte, die ja sonst bei weitem in der Minderzahl sind. Bekanntlich kommt es bisweilen auch bei essentieller Hypertonie vor, dass das Herz trotz langer Krankheitsdauer keine Hypertrophie zeigt (Fahr u. a.); indessen liegt diesbezüglich keine Angabe über die Verteilung nach Geschlechtern vor, zweifellos verdient aber dieser Faktor in diesem Zusammenhang Beachtung.

2. Kollateralbahnen für den Transport des Blutes nach den kaudalwärts von dem Hindernis gelegenen Körperteilen werden mittels Ästen des Subklaviasystems gebildet, nämlich teils der Mammaria interna, welche die Epigastrica-inferior-Gefässe begegnet, teils mittels des Truncus costocervicalis an der Innenseite des Thorax (besonders der Intercostalis suprema) und teils des Truncus thyreocervicalis sowie anderer Zweige an der Aussen- seite des Thorax (namentlich der Dorsalis scapulae), die durch die Interkostalararterien der Aorta descendens Blut zuführen. Dabei erweitern sich die Interkostalararterien und verlaufen serpiginierend (ein oft reproduziertes Bild von einem von Meckel beschriebenen Falle zeigt dies sehr anschaulich); durch den pulsierenden Druck gegen die hinteren Teile der Rippen kommt es dann zu Usuren an diesen, die sich röntgenologisch darstellen lassen. Die optimalste »Kollateral« bahn, die etabliert werden kann, ist die durch einen erhaltenen rechtsseitigen Aortenbogen (Arkin 1936, siehe im übrigen unten). Die direkteste Kollateralbahn, die im übrigen beschrieben worden ist, bestand in Wasastjernas Fall, wo bei einem 13-jährigen Knaben, der beim Schlittschuhlaufen durch eine Aortenruptur gestorben war, 4 recht grobe Arterien gleich

oberhalb der verengerten Stelle der Aorta ausgingen und gleich unterhalb davon wieder in diese einmündeten.

Pathologisch-anatomisch ist die Verteilung der Atheromatose von Interesse, die in dem vorliegenden Falle (1) zu verzeichnen war: Hochgradig in den Gefässen oberhalb, im wesentlichen nicht vorhanden in den Gefässen unterhalb des Hindernisses. Diese Verteilung scheint anzudeuten, dass der Blutdruck für das Zustandekommen der Atheromatose von Bedeutung ist; zwar war sie am ausgesprochensten in der Sinuscaroticus-Region, wo sie ja immer leicht auftritt, doch bestand ein unzweideutiger Unterschied zwischen der linken Art. subclavia, die dem höheren Druck ausgesetzt gewesen und atheromatös war, und der rechten, unterhalb des Hindernisses abzweigenden, die keinerlei Atheromatose aufwies. Dass in Fall (2) auch oberhalb des Hindernisses keine Atheromatose bestand, spricht mit Rücksicht auf die Jugend des Patienten nicht gegen diese Annahme. In Fall (3) wurde Arteriosclerose der grösseren Arterien nur oberhalb des Hindernisses angetroffen.

Pathogenese.

Die bei Neugeborenen beobachtete Form der Coarctatio mit einer allgemeinen Verengerung des Aortenisthmus wird seit Rokitsky allgemein einer Missbildung zugeschrieben, deren Entstehungsmechanismus folgendermassen gedacht wird. Im Embryonalleben des Menschen (ebenso wie auch extrauterin bei Tieren mit gemischtem Blutumlauf) werden der Kopf und der obere Teil des Körpers im wesentlichen durch die von der Konvexität des Aortenbogens ausgehenden drei grossen Gefässe versorgt, während dem unteren Teil des Körpers das weniger sauerstoffreiche Blut durch den Ductus Botalli zugeführt wird¹; der Teil des Aortenbogens, der zwischen der Abzweigung der Art. subclavia sin. und der Einmündung des Ductus Botalli liegt, wird daher nur wenig in Anspruch genommen und neigt deshalb dazu, in der Entwicklung zurückzubleiben, wodurch die Disposition für das Zustandekommen eines verengerten Gefässsegmentes geschaffen wird. Von einem bestimmten Interesse ist in diesem Zusammenhang der von Ask-Upmark (1935) hervorgehobene Umstand, dass die Aorta bei

¹ Hierdurch erklärt sich zweifellos grossenteils der Vorsprung der oberen Körperhälfte und namentlich des Kopfes in der Entwicklung.

vielen der grossen marinen Säuger (Zalophus, gewisse Wale usw.) eine Gestaltung zeigt, die in vieler Beziehung an diesen Koarktationstypus erinnert und möglicherweise für diese Tiere von blutdruckphysiologischer Bedeutung ist.

Die bei etwas älteren Kindern und bei Erwachsenen hauptsächlich auftretende, klinisch wichtigere Form der Coarctatio mit ihrer abrupten, wohlbegrenzten und oft hochgradigen Lumenverengung hat man auf die nämliche Art und Weise erklärt, soweit die Koarktation oberhalb der Einmündung in den Ductus Botalli lag. In der Mehrzahl der Fälle wiederum, wo sie in Höhe der Insertion des Botallischen Ligamentes oder unterhalb derselben gelegen war, hielt man die genannte Erklärung für unzutreffend und wollte stattdessen geltend machen, die Veränderung käme erst postnatal zustande, im Anschluss an die Involution des Ductus Botalli, dessen schrumpfendes Involutionsgewebe sich dann auch in die Aorta hinein erstreckte. Dass dies ausnahmsweise zutreffen kann, soll nicht abgestritten werden; ein in diesem Sinne sprechender Fall wurde von Bockdaleck schon 1845 beschrieben, und es sei gern zugestanden, dass die Annahme einer pränatalen Obliteration der Aortenlichtung unterhalb der Einmündung des Ductus Botalli hämodynamisch schlecht ohne gleichzeitigen Septumdefekt (der erwiesenermassen in der Regel fehlt) vorstellbar ist; Blackford geht in seiner sonst ausgezeichneten Analyse m. E. zu leicht über diesen Punkt hinweg. Andererseits scheinen die nachstehend aufgeführten Daten entschieden dafür zu sprechen, dass es sich bei der Coarctatio aortae um eine pränatale Missbildung handelt.

1. Koarktationen vom gleichen Typ wie bei Älteren hat man auch bei ganz kleinen Kindern gesehen (schon bei einem 8 Tage alten Kinde; siehe Blackford). Den bei Neugeborenen gewöhnlich begegnenden Typ hat man bisweilen auch bei Erwachsenen gesehen, oft in Verbindung mit dem hier üblichen Typ (z. B. bei Benkwitz und Hunter, 1937).

2. In den nicht ganz seltenen Fällen, wo die Koarktation so hoch oben am Aortenbogen wie bei oder gar proximal von dem Abgang der Art. subclav. sin. gelegen war, ist selbstverständlich ein vom Ligamentum Botalli übergreifender Schrumpfungsvorgang ausgeschlossen.

3. Coarctatio aortae vom »erwachsenen« Typus sieht man bisweilen in Verbindung mit einem noch offenen Ductus Botalli.

Obturierendes Ligamentgewebe kann also in diesen Fällen nicht mitgespielt haben.

4. Coarctatio aortae im hier verstandenen Sinne ist sehr oft mit anderen kardiovaskulären Missbildungen verbunden, wie zwei Aortenklappen statt drei, sowie mit Anomalien der von der Aorta ausgehenden Gefässstämme (vgl. oben).

Was den letztgenannten Punkt angeht, erscheint mir der in meinem ersten Falle beschriebene abnorme Ursprung und Verlauf der rechten Subklavia ganz besonders lehrreich. Dieser Anomalie haben die älteren Anatomen besondere Aufmerksamkeit geschenkt, und in verschiedenen Zusammenstellungen findet sich die Angabe, als solche (also ohne mit Coarctatio verbunden zu sein) komme sie in nicht weniger als 0.6—1.6 % vor (Hinweise bei Goldbloom 1922; aufschlussreich ist besonders Holzapfels Zusammenstellung von 200 einschlägigen Fällen). Teratogenetisch dürfte kein Zweifel daran bestehen können, dass eine solche Subklaviaarterie als der übriggebliebene distale Teil der im übrigen obliterierten rechten vierten Kiemenbogenarterie (rechten Aorta) anzusprechen ist; der Ursprung aus der Aorta unterhalb der linken Subklavia sowie auch der Verlauf hinter Oesophagus und Trachea sind charakteristisch. Nun hat man bei Koarktation diese Anomalie tatsächlich nicht selten vorgefunden: Abbott zitiert mehrere derartige Fälle (darunter Oppolzers 25-jähr. Apotheker), Blackford's Fall 12 zeigt prinzipiell den nämlichen Befund, und dasselbe gilt von einem von Love und Holms (1939) veröffentlichten Fall eines 44-jährigen Negers mit einem Blutdruck von 150/90 am rechten Arm, 210/95 am linken Arm, wo bei der Sektion festgestellt wurde, dass der rechte Arm den grössten Teil seines Blutes durch eine interkostale Verbindung zwischen der rechten Art. costocervicalis und der Aorta unterhalb des Hindernisses bekam. Tatsächlich fragt man sich, ob nicht in der Mehrzahl der Fälle von Coarctatio aortae dieser distale Teil des rechten Aortenbogens erhalten ist, scheinbar in Form einer Kollateralbahn von der Subklavia her (über die Art. intercostalis suprema). In diesem Zusammenhang sei an eine Untersuchung von Arkin (1936) über eine Anzahl von Fällen (6) mit doppeltem Aortenbogen erinnert; der rechte Bogen war wohl erhalten, während der linke eine ausgeprägte Koarktation aufwies; von dieser Stufe ist es nur noch ein Schritt zu den Fällen mit rechtsseitigem Aortenbogen allein (letztthin von Tengve 1941 beschrieben;

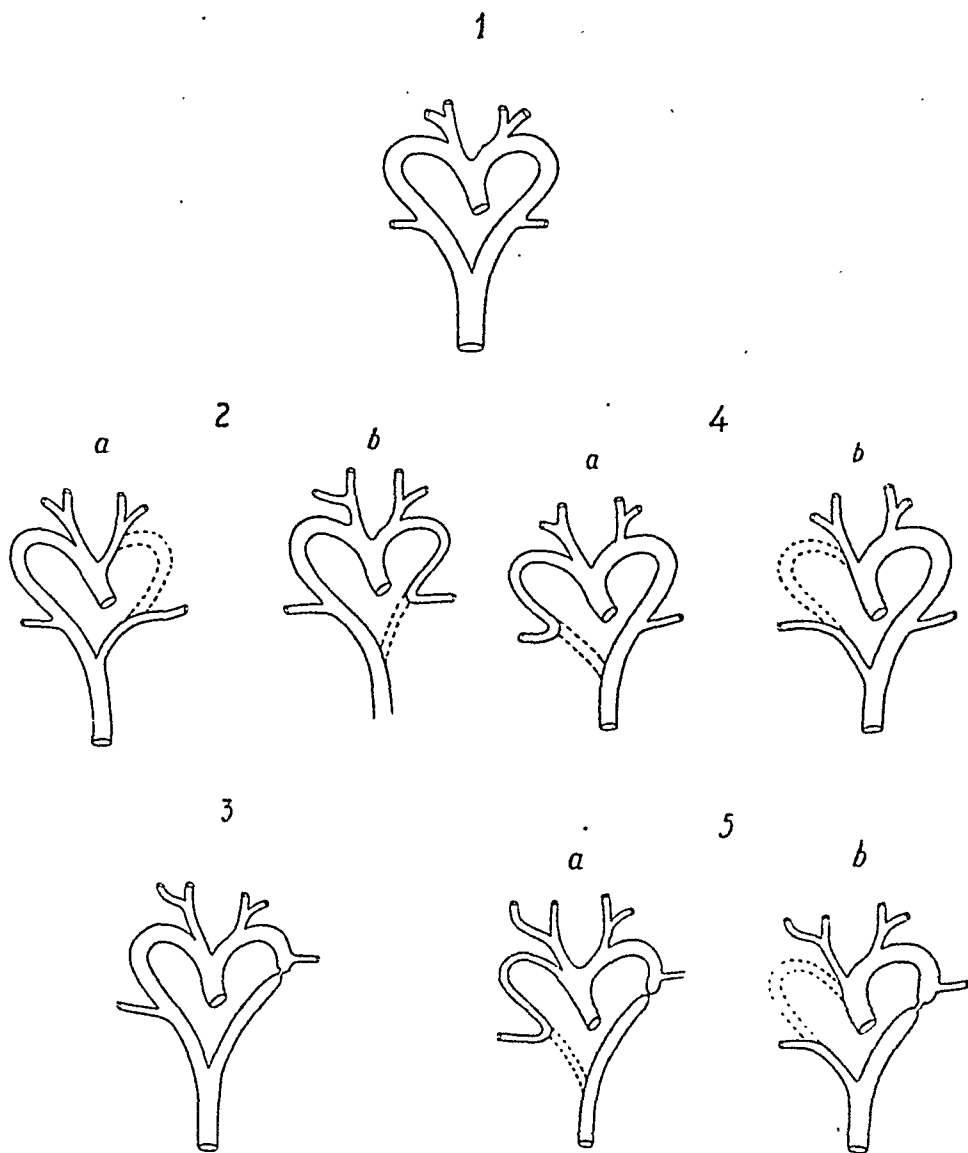


Fig. 7. Schematische Darstellung der formalgenetischen Entwicklung des Coarctatiozustandes:

1. Ursprüngliche Verhältnisse mit zwei Aortenbögen (Reptilien).
2. Rechtseitiger Aortenbogen beibehalten mit Ursprung der linken A. subclavia entweder als letzter (a) oder als erster (b) Ast des Bogens.
3. Rechtseitiger Aortenbogen, linksseitige Coarctatio (Arkin-Typus).
4. Linkseitiger Aortenbogen mit Ursprung der rechten A. subclavia entweder wie gewöhnlich als erster Ast (via Anonyma) oder in gewissen Fällen als letzter Ast des Bogens (a resp. b).
5. Coarctatio aortae a. unter gewöhnliche Verhältnisse b. unter Verhältnisse wie sie gemäss 4 b vorliegen und die von dem hier beschriebenen Fall 1 illustriert werden. Unter solche Bedingungen muss der Blutdruck am linken Arm hoch, am rechten niedrig sein.

siehe im übrigen Hinweise bei Arkin), wo die linke Subklaviaarterie entweder der letzte der brachiokephalen Äste der Aorta (Typ I; Spiegelbild des Subklaviaursprunges in meinem eigenen ersten Falle) oder der erste ist (Typ II; Spiegelbild des normalen Ursprunges der rechten Subklavia). Sieht man die Sache so, kann der Zustand mit zwei viablen Aortenbögen (Reptilmodell) als der Urtyp gelten. Normal bleibt beim Menschen der linke bestehen, während der rechte im wesentlichen zur Art. subklavia wird (Säugermmodell); eine Spielart dieses Typs ist der Ursprung der rechten Subklavia als letzter brachiokephaler Arterienstamm. Andererseits kann statt dessen der rechte Aortenbogen persistieren (Vogelmodell), während der linke der Involution verfällt und nur als Subklavia fortbesteht, die dann auf zweierlei Weise aus der rechtsorientierten Aorta entspringen kann, nämlich als erster brachiokephaler Zweig oder als letzter. Der rechte Aortenbogen wird sozusagen normalerweise von Coarctatio in Form von Involution gewöhnlich seines distalen, bisweilen seines proximalen Teiles betroffen. Die Koarktation kann indessen auch den linken Aortenbogen befallen, besonders natürlich wenn der rechte entwickelt ist, bisweilen aber auch bei rückgebildetem oder — vielleicht richtiger ausgedrückt — nicht genügend entwickeltem rechten Aortenbogen; ist der rechte Subklaviaursprung dann normal, so ergeben sich die bei Coarctatio gewöhnlichen Verhältnisse, zweigt die Subklavia als letzter brachiokephaler Stamm ab, so ergibt sich das Bild, das wir in meinem Falle (1) sahen.

Offensichtlich kann eine rechte Subklavia dieses Typs bisweilen als Kollateralbahn an dem Hindernis vorbei dienen, unter der Voraussetzung nämlich, dass sie unterhalb des Hindernisses die Aorta verlässt und dass sie auf Anonymaäste stösst. Andererseits liegt es auf der Hand, dass das Vorhandensein einer Subklaviaarterie von dieser Beschaffenheit in keiner Weise durch die Koarktation als solche verursacht ist: teils kommt dieser Subklaviatyp ja ohne gleichzeitige Koarktation vor, teils liegen die Verhältnisse bisweilen so, dass sie nicht als Kollateralbahn dienen kann: in meinem Falle besorgte sie allein die Nutrition des rechten Armes, ohne sichtbare Hilfe seitens anonymer Äste, in Oppolzer's Fall ging sie zwar als letzte brachiokephale Arterie von der Aorta aus, doch oberhalb des Hindernisses. Wir müssen also zu dem Schluss kommen, dass wir es hier mit einem präformierten Zustand zu tun

haben, der zusammen mit Coarctatio aortae vorkommen kann (und sicherlich oft in abortiver Form vorkommt).

Teratogenetisch ist also festzustellen, dass eine postnatale Entwicklung der Koarktation im Anschluss an die Obliteration des Ductus Botalli unwahrscheinlich ist, während dagegen mit überwiegender Wahrscheinlichkeit eine Entwicklung des Zustandes im Anschluss an die endgültige Ausbildung der Kiemenbogenarterien im zweiten Embryonalmonat anzunehmen ist. Wie sich die Entwicklung im einzelnen gestaltet, lässt sich natürlich schlecht sagen: sicherlich spielt die von Rokitansky hervorgehobene Differenzierung der Blutversorgung für die obere und die untere Körperhälfte eine Rolle, wahrscheinlich auch andere Faktoren: so soll darauf hingewiesen werden, dass ein obliterierender Involutionsvorgang, wie er sich postnatal im Ductus Botalli vollzieht, bereits auf dieser embryonalen Stufe in enger Anlehnung an die Aortenbögen vor sich geht, nämlich im Ductus caroticus; die Involution des proximalen rechten Subklaviateiles in Fällen vom Schlage meines Falle (1) ist hier möglicherweise eine Parallelerscheinung zur Koarktation; ferner sei an die mögliche Bedeutung des querlaufenden linken Hauptbronchus (vgl. die Oesophagusverengung in gleicher Höhe sowie die Kaudalverschiebung des Herzens zu diesem Zeitpunkt), des linken Recurrensnerven und der Lageveränderungen des Verdauungskanals erinnert [vgl. die eigentümliche Erscheinung, dass bei erhaltenem doppelseitigem Aortenbogen der linke in der Regel von kleinerem Kaliber ist als der rechte (Arkin)]. Wenn ein leerer¹ Schlauch (die Isthmuspattie) über eine Kante (den linken Bronchus bzw. Recurrens am Descensus des Herzens?) gebogen wird, so müssen besonders günstige Bedingungen für eine Obliteration vorliegen, und zwar vielleicht um so mehr, als der eng angeschlossene, ebenfalls unbeschäftigte Ductus caroticus hier mit gutem Beispiel vorangeht.

Von diesen selbstverständlich stets hypothetischen formal-genetischen Einzelheiten abgesehen, dürften wir indessen zusammenfassend feststellen können,

dass die Coarctatio aortae pränatalen Ursprungs ist,

dass der teratogenetische Terminationspunkt wahrscheinlich im 2. Embryonalmonat zu suchen ist, sowie

¹ Der Begriff »leer« ist natürlich nicht allzu buchstäblich zu fassen; hydrodynamisch liegt es nahe, in diesem Gebiet das Vorhandensein der als »plasma skimming« bezeichneten Erscheinung anzunehmen.

dass der formalgenetische Entstehungsmechanismus sich eng an die Differenzierung der Kiemenbogenarterien anlehnt, ganz besonders offenbar an die Erhaltung eines (mehr oder weniger abortiven) rechtsseitigen Aortenbogens.

Physiologie.

Physiologisch ist die *Coarctatio aoriae* vor allem durch das eigentümliche Verhalten des Blutdruckes von Interesse. In der Regel ist der Blutdruck oberhalb des Hindernisses (also in Armen, Kopf usw.) stark erhöht, unterhalb der Hindernisses (also in den Beinen) dagegen gesenkt. In einigen Fällen war auch der Blutdruck der Beine einwandfrei erhöht. In seltenen Ausnahmefällen wurde auch in den Armen normaler Blutdruck festgestellt.

Beim normalen Menschen soll der Blutdruck vor dem 30. Lebensjahre in Armen und Beinen gleich sein, nach diesem Alter ist der Blutdruck der Beine höher. Besonders auffällig ist dieser Niveauunterschied zwischen Armen und Beinen bei Aorteninsuffizienz (Hill'sches Phänomen), während er andererseits bei Infekten oder Herzmuskelschäden besonders geringfügig oder gar umgekehrt sein kann (Naumann 1939, dort Schrifttumsnachweise).

Die Hypertonie der oberen Körperhälfte bei *Coarctatio aortae* ist von mehreren Forschern in den letzten Jahren einer peripheren Vasokonstriktion, humoral durch eine renale Ischämie ad modum Goldblatt herbeigeführt, zugeschrieben worden (Goldblatt et al. 1939, Steele 1939, Page 1940, u. a.). Dieser im wesentlichen auf Analogien aus Tierversuchen (Konstriktion der Aorta oberhalb bzw. unterhalb der Nierenarterie) fussenden Auffassung lassen sich indessen die folgenden Einwände entgegenhalten.

1. Die durch Konstriktion der Aorta abdominalis oberhalb des Ursprungs der Nierenarterien experimentell hervorgerufene Hypertonie weist zwar unverkennbare Übereinstimmungen mit der durch Konstriktion der Nierenarterien bewirkten Hypertonie auf, doch ist sie vorübergehender Natur. Bei der *Coarctatio aortae* dagegen ist die Blutdruckerhöhung konstant, wenn nicht das Herz versagt.

2. Durch direkte Beobachtungen an Fällen mit *Coarctatio aortae* hat man zeigen können, dass die Reaktionsbereitschaft der Gefäße gegenüber verschiedenartigen Impulsen in der oberen und der unteren Körperhälfte die gleiche ist (Woodbury-Murphy-

Hamilton 1940). Demgemäss wäre, falls ein renaler Ursachenfaktor vorläge, eine Hypertonie nicht allein der oberen, sondern auch der unteren Körperhälfte zu erwarten, da der verantwortliche Mechanismus eine Vasokonstriktion wäre, also ein Widerstandshochdruck. Dies ist aber bei der Koarktation in der Regel nicht der Fall: der Blutdruck der Beine ist in der grossen Mehrzahl der Fälle normal oder niedriger als normal. Nun könnte man einwenden, dass wenn die Kollateralbahnen das Blut nur unvollständig in die untere Körperhälfte zu schaffen vermögen, hier eine Vasokonstriktion vorliegen könnte, ohne dass diese sich in einem zu hohen Druck zu äussern brauchte. Teils aber liegen in der grossen Mehrzahl der Fälle von Coarctatio aortae keinerlei klinische Anhaltspunkte für eine mangelhafte Blutversorgung der unteren Extremitäten vor (die Ausnahmen sind selten und bestätigen die Regel), teils auch muss die Berechtigung dessen, das primären Vorhandensein eines Widerstandshochdruckes anzunehmen, überhaupt in Frage gestellt werden.

3. Wäre nämlich ein Widerstandshochdruck durch periphere Vasokonstriktion das Wesentliche bei Coarctatio aortae, so würde man erwarten, dass der diastolische Druck in den Armen konstant zu hoch wäre. Das ist aber durchaus nicht der Fall. Eine Zusammenstellung von King (1937) über den Blutdruck in den bis dahin veröffentlichten Fällen von Aortenkoarktation zeigt folgendes: unter 146 Fällen mit gemessener systolischer Armhypertonie war der diastolische Druck in 32 Fällen (darunter 10 Frauen) 80 oder unter 80, während er in 56 Fällen (darunter 22 Frauen) 100 oder höher war. Ein durchweg begegnender Zug war ferner die auffallend hohe Blutdruckamplitude.

Ganz besonders mit Rücksicht auf den oft normalen diastolischen Armblutdruck (vgl. meine eigenen Fälle) ist zweifellos eine Widerstandshypertonie in dem von Wezler umrissenen Sinne dieses Wortes bei dem in Rede stehenden Zustand als weniger wahrscheinlich anzunehmen. Das Schlag- und Minutenvolumen des Herzens verhält sich andererseits im wesentlichen normal; es kann etwas vergrössert sein, ist aber in der Regel normal (Stewart und Bailey, 1941; Erwähnung verdient hier der Befund derselben Autoren, dass der Grundumsatz in 3 Fällen erhöht, in 1 gesenkt und in 5 Fällen normal war); eine Minutenvolumenhypertonie liegt also kaum vor. Dagegen scheinen sich sowohl der normale

diastolische Druck als die grosse Pulsamplitude gut mit der Annahme einer Elastizitätshypertonie im Sinne Wezlers, also einer ungenügenden Windkesselfunktion, in Einklang bringen zu lassen. Bei den jungen Menschen, um die es sich hier meist handelt, dürfte zwar die Elastizität der grossen Gefässe nicht direkt bezweifelt zu werden brauchen (vgl. jedoch die Befunde präformierter Veränderungen der Aortenwand), dagegen aber dürfte zweifellos durch die Coarctatio Veränderung eine starke Verkleinerung des Windkesselvolumens eingetreten sein (vgl. Herkel, 1939). Es würde hier also mit anderen Worten ein hämodynamisches Gegenstück den von Dietrich beschriebenen Fällen von juveniler Hypertonie bei enger Aorta vorliegen (siehe Wezler). Diese Annahme steht in vollem Einklang mit den anatomischen Verhältnissen ebenso wie mit den oben angegebenen physiologischen Merkmalen der festgestellten Hypertonie. Der Mechanismus wäre also eine Parallele zu dem von Wezler bei essentieller Hypertonie angenommenen; dass sekundär ein Widerstandshochdruck hinzutreten kann, dann mit einer Erhöhung auch des diastolischen Druckes, erscheint bei der Koarktation ebenso natürlich wie bei essentieller Hypertonie, und der bisweilen erhöhte Grundumsatz legt naturgemäss auch die Kombination mit Volumenhochdruck nahe. Der Kern der bei Coarctatio aortae bestehenden Hypertonie aber wird das verminderte Windkesselvolumen ausmachen, also eine Variante des Elastizitätshochdruckes.

In denjenigen Fällen von Coarctatio, wo auch der Blutdruck der unteren Extremitäten erhöht ist, dürfte man das Vorhandensein besonders direkter und wohlentwickelter Kollateralbahnen anzunehmen haben; liegt diastolische Hypertonie vor, so wird sich offenbar ein Widerstandshochdruck durch periphere Vasokonstriktion hinzugesellt haben. Vom praktischen Gesichtspunkt ist es in dieser Hinsicht von Gewicht, dass der Befund der Hypertonie an den unteren Extremitäten nicht die Diagnose Coarctatio aortae ausschliesst, nicht einmal wenn der (für Coarctatio) exzeptionelle Fall eintreten sollte, dass der Blutdruck der Beine höher ist als der Armblutdruck (wie in einem von Stewart und Baileys autopsisch gesicherten Fällen: 48 jährige Frau mit 255/160 am Arm, 290/200 am Bein gemessen).

Andererseits scheint in seltenen Ausnahmefällen der Blutdruck der oberen Körperhälfte bei Coarctatio normal sein zu können.

nen. King (1937), der diese Frage untersucht hat, findet bei sorgfältiger Durchmusterung des Schrifttums nur einen einzigen solchen Fall, eine 25 jährige Frau, von ihm selbst beschrieben, wo der Blutdruck beider Arme sich in normalen Grenzen hielt (die Pulsamplitude war jedoch gesteigert); in den übrigen beschriebenen Fällen mit normalen oder niedrigem Blutdruck der oberen Körperhälfte war entweder eine vorhandene Dekompensation für die Senkung verantwortlich, oder auch der Blutdruck war nur an dem einen Arm gemessen worden. Letzteres kann indessen irreführend sein: in mehreren Fällen war nämlich der Blutdruck des linken Armes niedriger als der des rechten und in gewissen Fällen sogar normal (der systolische häufiger als der diastolische). Bekanntlich kommt beim normalen Menschen oft ein Unterschied zwischen dem Blutdruck der beiden Arme vor (Schrifttumsnachweise bei King; siehe auch Southby 1935); in diesen Fällen ist ebenfalls der Druck am rechten Arm in der Regel höher als der am linken, doch ist der Unterschied bedeutend geringer als in den hier in Rede stehenden Fällen von Coarctatio, bei denen man möglicherweise annehmen darf, dass die Veränderung ihren Sitz vor dem Abgang der linken Subklavia hat, was ja bisweilen der Fall sein kann. Wenn in den besagten Fällen der Blutdruck nur am linken Arm gemessen worden ist, muss man die diagnostisch so wichtige Hypertonie übersehen. King nennt andererseits einen ihm unerklärlichen Befund von East, wo der Druck im rechten Arm bedeutend niedriger als im linken und sogar niedriger als im Bein war. Dieser Fall, der nicht zur Autopsie gekommen war, lässt sich m. E. gut erklären, indem man eine Anordnung der Gefäße annimmt wie sie in meinem Falle (1) vorlag: Ursprung der rechten Subklavia unterhalb des Hindernisses.

Physiologisch ist ferner der Umstand von Interesse, dass die Nierenfunktion bei Fällen von unkomplizierter Coarctatio aortae intakt zu sein scheint (Beisp.: Flexner: 19-jähr. Mann mit urea clearance 106.6 %, R. N. 27; Herkel: 41-jähr. Mann mit der Harnkonzentration 1,028). Schliesslich sei auf den in der Literatur wiederholt hervorgehobenen Befund eines erhöhten Grundumsatzes bei diesen Fällen hingewiesen, wobei sie Züge annehmen können, die an die Basedow'sche Krankheit erinnern; doch sei unterstrichen, dass der Grundumsatz meistens normal zu sein scheint (vgl. Stewart und Bailey).

Klinik.

Die Coarctatio aortae kann sich klinisch in verschiedener Weise verhalten.

1. Bisweilen entdeckt man den Zustand als Nebenbefund bei der Obduktion, ohne dass er zu Lebzeiten, soweit bekannt, subjektive Beschwerden verursacht hätte oder mitverantwortlich am Tode gewesen wäre.

2. In anderen Fällen manifestiert sich die Koarktation in der Form des plötzlichen Todes eines anscheinend gesunden Menschen. Die Todesursache ist in diesen Fällen entweder eine vaskuläre Hirnläsion oder eine Aortenruptur oder in Herztod s.str.

3. Schliesslich verursacht die Coarctatio aortae in vielen Fällen mehr oder weniger lange Zeit vor dem Tode Krankheitserscheinungen. Diese sind im ganzen von zweierlei Art, einerseits Hypertoniebeschwerden seitens des Kopfes oder des Herzens, andererseits Symptome einer komplizierenden Endokarditis (oft vom Typus der *E. viridans*); bisweilen kann auch ein Morbus Basedowi vorgetauscht werden, was sogar ein operatives Eingreifen veranlassen kann. Nur in seltenen Ausnahmefällen bestehen Symptome mangelhafter Blutversorgung der unteren Extremitäten (Claudicatio und andere Beschwerden; bisweilen das sog. Evans'sche Symptom: wenn der Patient sich aus der liegenden Stellung erhebt, bemerkt er eine eigentümliche Schwäche und Gefühllosigkeit der Beine, die beim Gehen bald verschwindet).

Die objektive Untersuchung erhebt vor allem drei charakteristische Befunde.

1. Erhöhter Blutdruck in den oberen Extremitäten, verhältnismässig niedriger Blutdruck in den unteren. Obwohl diese Konstellation nicht durchaus konstant ist (vgl. oben), so ist sie doch die Regel bei Coarctatio. Da es sich gewöhnlich um junge Menschen handelt, hat man diagnostisch in allen Fällen von juveniler Hypertonie auch die Möglichkeit der Coarctatio aortae ins Auge zu fassen. Es sei an die Notwendigkeit dessen erinnert, den Blutdruck an beiden Armen wie auch an den Beinen zu messen. Der Puls der Art. femoralis ist in der Regel parvus, tardus und stark verspätet; in Ausnahmefällen kann er indessen wohlgefüllt sein. Hervortretende Pulsationen am Halse. Uhrglasnägel und Trommelschlägelfinger

können vorkommen: lehrreich war in dieser Beziehung mein eigener Fall (1) mit Uhrglasnägeln an der linken, nicht aber an der rechten Hand (versorgt aus der Aorta oberhalb bzw. unterhalb des Hindernisses); die Veränderungen stehen selbstredend mit der Dilatation der Nagelkapillaren im Zusammenhang.

2. Die Entwicklung der kollateralen Arterien lässt sich oft, doch nicht immer durch Palpation und Inspektion feststellen. Namentlich das Gebiet medialwärts der Scapula ist sorgfältig zu untersuchen, ganz besonders in Höhe des Angulus: der Befund gänsefederweiter, pulsierender subkutaner Arterien an dieser Stelle ist für die Coarctatio pathognomonisch. Ebenso Dilatation der Mammaria interna — das Epigastrica-System projiziert sich bisweilen auf die Haut. In den Fällen wiederum, wo der Truncus costovertecalis mit dem Intercostalis-suprema-System die wesentliche Kollateralbahn bildet, kann man an dem Kranken in der Regel keine direkten Kollateralbahnen feststellen; dagegen sieht man sowohl in diesen als oft auch in anderen Fällen eine zuerst von Rösler (1927) beschriebene röntgenologische Usur des hinteren Teiles der Rippen, und zwar am unteren Rande derselben, wo die Interkostalarterien bei ihrer Erweiterung eine Druckatrophie erzeugen; anatomisch wurde dieser Befund 100 Jahre vor Rösler von Meckel erhoben. Diese Rippenusuren sind ebenfalls für die Coarctatio pathognomonisch.

3. Das Herz zeigt in der Regel eine starke Linkshypertrophie, oft in Verbindung mit Dilatation, ferner systolische Geräusche, von denen das charakteristischste ein stark im Interskapularraum hörbares Geräusch ist. Obwohl man gesagt hat, die Coarctatio aortae sei die einzige kongenitale Missbildung, die mit einer reinen Linkshypertrophie verbunden sei, dürfte die physikalische Untersuchung allein nur ausnahmsweise wegweisend sein. Elektrokardiographisch verzeichnet man ein ebenfalls nicht spezifisches Linksübergewicht, bisweilen im Verein mit Zeichen einer Myokardschädigung. Röntgenologisch lässt sich indessen, wie Wolke (1937) hat zeigen können, bisweilen direkt eine für Coarctatio charakteristische Indentierung des Aortenschattens feststellen, die bei schräger Durchleuchtung, besonders gut mit Kontrast in der Speiseröhre, sichtbar ist.

Prognose und Therapie:

Auf die Prognose wurde oben (S. 12) eingegangen: der Zustand ist in sehr hohem Grade dazu angetan, das Leben zu verkürzen, andererseits aber muss man sich klar sein, dass wie Lewis hervorgehoben hat, »failure is not inevitable«. Es gibt Fälle, die ein hohes Alter erreicht und ein sehr aktives Leben gelebt haben.

Die Therapie muss im wesentlichen prophylaktisch sein. Wie bei den übrigen Herzaffektionen, Klappenfehlern und Herzmuskel-schäden, so gilt es auch von der Coarctatio aortae, dass die beiden grossen Gefahrenmomente Überanstrengung und Infektionen heissen. Die Berufswahl ist bei diesen jüngeren Menschen von sehr grosser Bedeutung. Ist Dekompensation eingetreten, so dürfte die Prognose in der Mehrzahl der Fälle ominös sein, da das Herz ja bereits seine gesamte verfügbare Kraft verausgabt hat. Chirurgischer Therapie dürfte die Coarctatio aortae einstweilen noch unzugänglich sein.

Summary and conclusions.

1. Three cases of aortic coarctation, recently observed at the Medical Clinic of Lund, are described: a) man, aged 32, death caused by endocarditis lenta, aortic coarctation + bicuspid aortic valve + origin of right subclavian artery below the coarctation; b) man, aged 18, death caused by pulmonary tuberculosis, diagnosis of aortic coarctation established during life; weight of the heart 1,400 gram; c) man, aged 69, death caused by cardiac failure; aortic coarctation.

2. A brief review is given of the history, the occurrence, the anatomy, the physiology and the symptomatology of the aortic coarctation. Attention is called to the occurrence of a somewhat similar condition in the aorta of several big aquatic mammals, as demonstrated by the author in 1934. With regard to the frequency our attention has been drawn to the possibility of encountering aortic coarctation during the last decade. During this decade more than 30,000 patients have been treated in the Medical Clinic and more than 5,000 necropsies carried out at the Institute of Patho-

logy. The three observations here described were the only ones encountered in Lund since 1897, when Wadstein called attention to the matter.

3. Aortic coarctation should be looked upon as a malformation of prenatal origin, reasonably developing before the end of the second month of gestation. With regard to the formal teratogenesis particular attention should be called to frequent occurrence of a more or less differentiated right aortic arch, usually manifesting itself as a low origin of the right subclavian artery.

4. The behaviour of the blood pressure in aortic coarctation is discussed from the hemodynamic point of view. The regular occurrence of hypertension in the upper half of the body should be looked upon as an «elasticity-hypertension» in the sense of Wezler, depending upon a reduction of the volume of the windkessel. Additional secondary factors may sometimes be increased peripheral resistance (by means of a Goldblatt mechanism) and increased cardiac output (in cases with increased basal metabolism).

5. Aortic coarctation should be looked for on the one hand in cases of sudden unexpected death in young, apparently healthy individuals, on the other hand in instances of juvenile hypertension as well as when endocarditis lenta is about. Appropriated selection of profession seems to be important.

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Auricular extrasystoles inducing auricular fibrillation in acute infectious diseases.

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Introduction.

The fact of auricular extrasystoles often preceding auricular fibrillation in myocardial disease is well established [Wenckebach and Winterberg (1); Scherf (2)]. Scherf even advises quinine treatment in conditions known as liable to be complicated by auricular fibrillation, such as mitral stenosis, coronary sclerosis, hyperthyroidism, when the patients begin to show auricular extrasystoles. In this author's opinion, extrasystoles which show continually varying shapes of P-deflexion are often the predecessors of auricular fibrillation. A striking instance of transitory auricular fibrillation, introduced by blocked auricular extrasystoles, is given on p. 150 and 151 of his above-mentioned study.

Auricular extrasystoles and auricular fibrillation in infectious disease.

We were struck by the fact that patients with Sumatran leptospiral infection and with pneumococcal pneumonia sometimes show auricular fibrillation. In all we saw this happen in two cases of leptospirosis and three of pneumonia; as we think the knowledge of this

connection to have some importance for the prognostic valuation of the heart action in infectious disease, we want to communicate this observation.

Leptospiral infection [Sumatra (3)].

These infections are to be considered as a variant of Weil's disease. Fig. 1 shows a temperature chart of a patient, on which the onset of extrasystoles and auricular fibrillation are indicated. In this

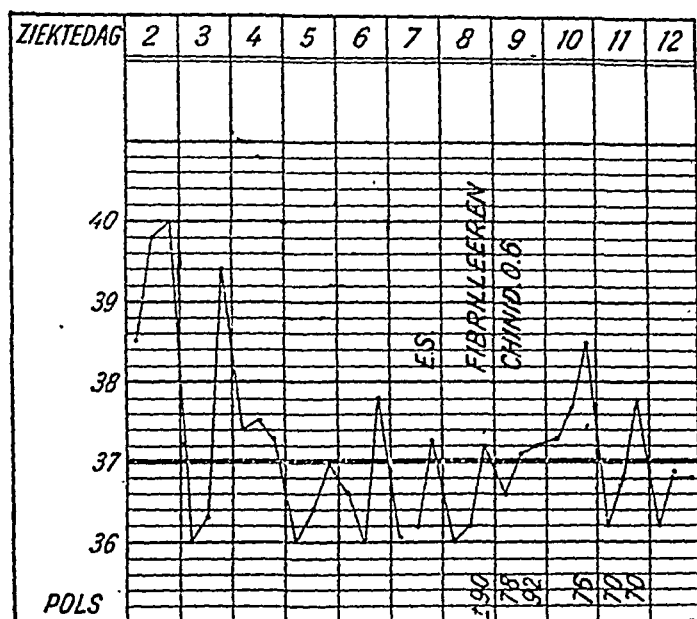


Fig. 1. Temperature chart and pulse in leptospiral infection. (Ziekte dag = day of illness. E.S. = extra-systoles. Fibrilleeren = fibrillation. Pols = pulse).

case no tracing was made of the extrasystoles. The diagnosis of auricular fibrillation was made in view of the completely irregular arterial pulse, in the absence of a-waves in the jugular pulse. The fibrillation lasted for one day; on the subsequent day the a-c interval of the jugular pulse was somewhat lengthened, in which a sign of myocarditis must be seen. The patient was given 0.6 g of quinidine sulphate from the onset of fibrillation. This observation led us to observe more closely the second case of this kind.

Chart 2 gives the temperature curve of this case with the clinical data of the heart action. Fig. 3 shows the auricular extrasystoles. The fibrillation came in attacks, which sometimes were of very

brief duration (fig. 4). In fig. 4 it is probable that the fibrillation was induced by a blocked auricular extrasystole. After the c-wave of the last normal cycle, a higher wave follows prematurely, probably representing the summation of a and v.

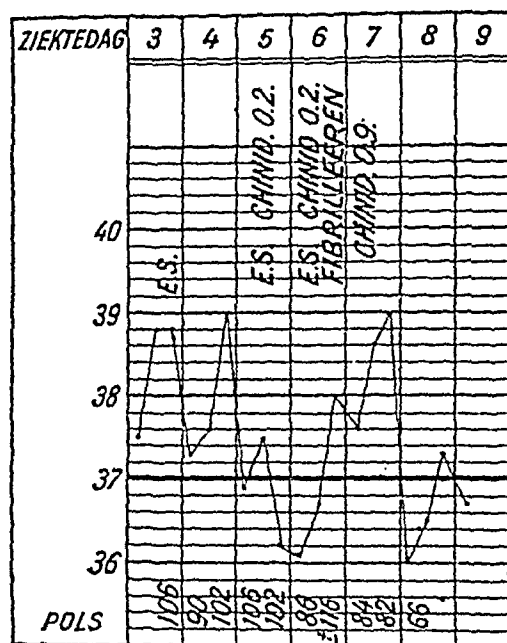


Fig. 2. Temperature chart and pulse in leptospiral infection.

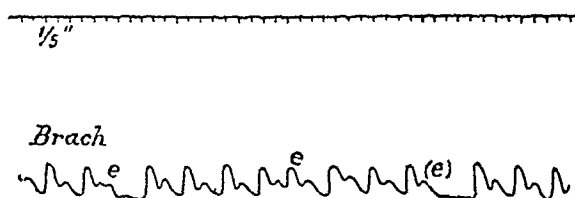


Fig. 3. Auricular extra-systoles in leptospiral infection (case of fig. 2).

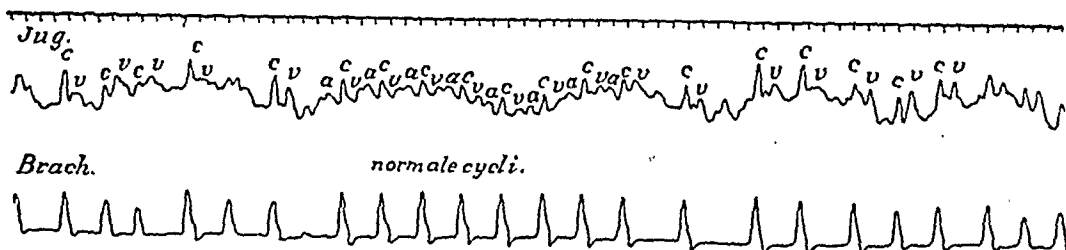


Fig. 4. Auricular fibrillation, interrupted by a brief period of normal sinus rhythm (case of fig. 2).

Pneumococcal pneumonia.

Fig. 5 shows the temperature chart of a patient with pneumococcal pneumonia with the clinical data concerning the pulse. Fig. 6 and 7 give the obtained pulse tracings. Again auricular fibrillation

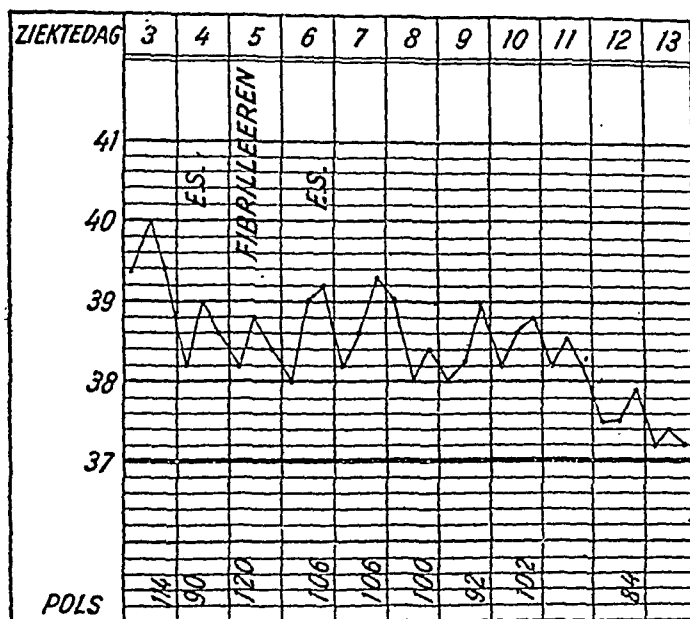


Fig. 5. Temperature chart and pulse in pneumonia.

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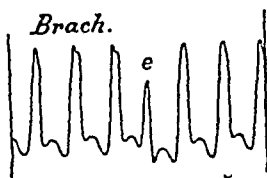


Fig. 6. Auricular extra-systole (Pneumonia, case of fig. 5).

was preceded by auricular extrasystoles, which was also seen to persist after the period of fibrillation. The patient recovered after a long illness (observation in the tropics in 1927).

The analysis of the next case gives us an insight into the connection between both types of irregularity. Fig. 8 shows the clinical data.

The patient, a man aged 47, formerly healthy, suffered from pneumococcal pneumonia with bacteriaemia (type 1) and was treated intra-venously with specific antiserum. On the third day of illness supraventricular extrasystoles set on, with a fixed linking in terval of 0.32 sec. and somewhat aberrant ventricular potentials (fig. 9).

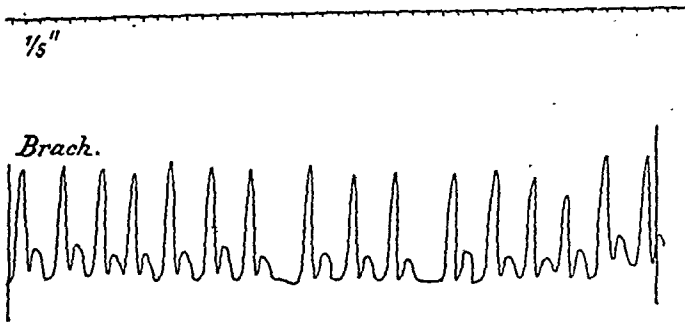


Fig. 7. Completely irregular pulse (auricular fibrillation). (Pneumonic, case of fig. 5).

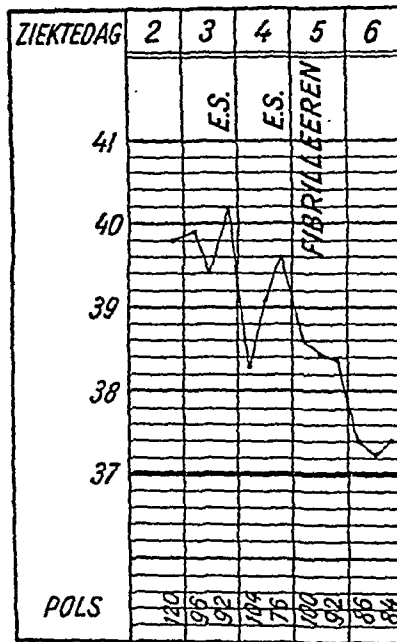


Fig. 8. Temperature chart and pulse in pneumococcal pneumonia.

The form of the premature P (P^1) was nearly that of a normal P, so that it may be assumed that the extrasystoles took their origin in or quite near the sinus node. The onset of these extrasystoles gave reason to expect fibrillation to develop. On the 5th day of illness we found a very irregular pulse as a result of auricular fibrillation.

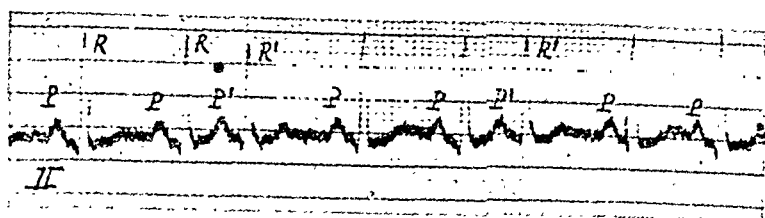


Fig. 9. Auricular extra-systoles in pneumococcal pneumonia (case of fig. 8).

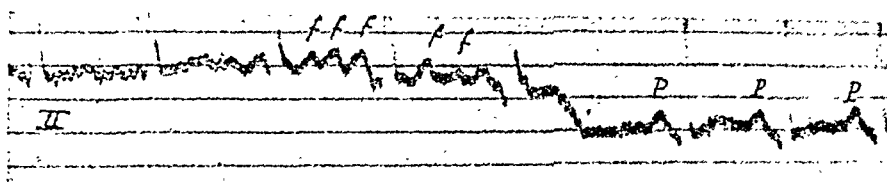


Fig. 10. End of attack of auricular fibrillation in pneumonia (case of fig. 8).

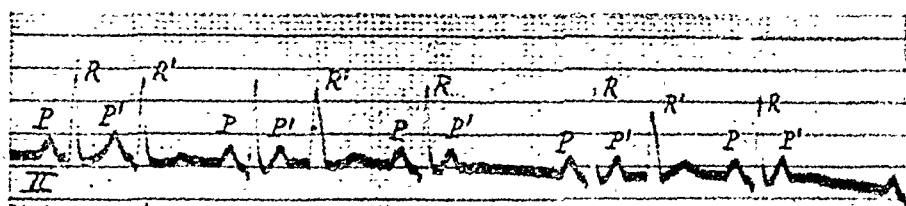


Fig. 11. Blocked auricular extra-systoles in pneumonia (case of fig. 8).

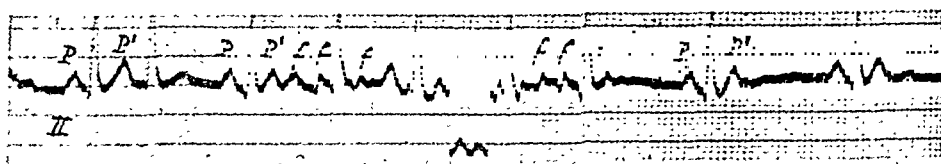


Fig. 12. Short attack of auricular fibrillation, induced by a blocked auricular extra-systole (case of fig. 8).

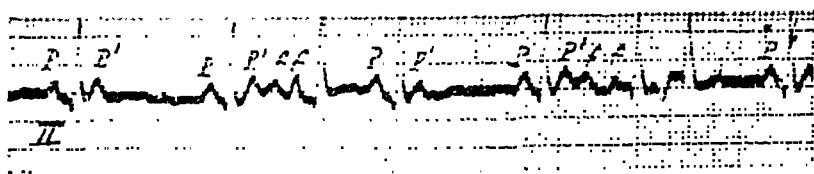


Fig. 13. Very short periods of auricular fibrillation, induced by blocked auricular extra-systoles (case of fig. 8).

Electrocardiographic analysis of long tracings revealed the fibrillation to be replaced by periods of normal sinus rhythm from time to time, which then, however, was continually disturbed by auricular extrasystoles. Twice the transition of fibrillation into normal sinus rhythm could be traced. During the last moments of fibrillation large auricular deflections appeared, so that the curve took a resemblance to auricular flutter (fig. 10). Most interesting was the transition from sinus rhythm into fibrillation, which could be beautifully followed up in one of the tracings: after the cessation of a paroxysm of fibrillation a sinus rhythm appeared with numerous auricular extrasystoles, which at first showed constantly the same linking interval of 0.32 sec. as was found on the previous day. After 30 seconds this interval was suddenly shortened to 0.24 sec., after which there came two cycles with very aberrant ventricle complexes after a protracted conduction time. (fig. 11). The shape of the premature P^1 was somewhat different from that of the P^1 waves with a longer linking interval. Now there came a period in which all auricular systoles were blocked at the atrioventricular junction. The duration this period could not be ascertained exactly, but anyway very shortly afterwards the tracing began to show sections in which a blocked auricular extrasystole induced a brief attack of auricular fibrillation with rather high electric potentials («impure» flutter). Sometimes, after the extrasystolic P^1 , only two of these fibrillation waves appeared, after which they were again replaced by the sinus rhythm (fig. 12 and 13). The whole period of fibrillation lasted on the 5th day of illness till 3 p. m., after which the pulse became regular again and remained so.

We still saw this course of events in another patient with pneumococcal pneumonia, in whom it could not be studied with the same accuracy, and once more in a patient with severe bleeding from a peptic ulcer. In the latter the auricular extrasystoles preceding the fibrillation were not blocked, which shows that the extrasystoles do not always induce fibrillation in the same way.

Pathogenesis of auricular fibrillation in the present cases. De Boer's experiments.

The above observations show a striking agreement with the experimental pathology of auricular fibrillation. It is well-known

that the Boer (4) could induce ventricular fibrillation in the bled frog-heart with a single faradic stimulus, if only the following conditions were fulfilled:

1. There must be accessibility to fibrillation. This exists during a quite definite time after blood-withdrawal.

2. The faradic stimulus must be applied immediately after the end of the refractory phase of the ventricle.

Ventricular fibrillation could not only be induced by artificial faradic stimulation, but in some experiments a premature stimulus originating from the auricle could also produce it. In the atrium of the frog-heart, too, De Boer could start fibrillation in the same way. For details and theoretic considerations we refer to De Boer's publications. This author already draws an analogy between this observations and auricular fibrillation in man, and supposes accelerated sinus activity to be able in some cases to produce fibrillation (after severe exertion, in Graves's disease etc.).

It is obvious that these experiments could be made use of in giving a partial explanation of the above clinical observations. We must assume that during a certain phase of the infectious diseases in question the auricular muscle was in a condition which made it accessible to fibrillation. When during such a phase supraventricular extrasystoles arise, a single premature impulse, arising just after the refractory period of the atrium, can induce fibrillation. The electrocardiographic analysis of the above described case indeed shows that in some cases there is a probable connection between the degree of prematurity of the auricular stimulus and the inducing of fibrillation.

These considerations, of course, cannot explain the whole course of events; particularly it is uncertain whether the accessibility to fibrillation is a phenomenon correlated with the arising of extrasystoles, but to these questions only a speculative answer can be given.

It is probable that in the above cases there was myocarditis in the anatomical sense. The first case of leptospirosis, which later showed a lengthened a-c-interval, is demonstrative of this condition. The myocarditis of Weil's disease is well-known anatomically, which is also the case with pneumococcal pneumonia.

Ventricular fibrillation and sudden cardiac death in the above infectious diseases.

In concluding, we must ask ourselves, to which extent the heart in patients with infectious diseases, who show auricular extrasystoles and auricular fibrillation, is also liable to the arising of ventricular fibrillation, which event we know to be far less easily provoked than auricular fibrillation.

In Weil's disease sudden cardiac death is only too well-known; in pneumonia, on the contrary, it is much rarer. Most probably in such cases ventricular fibrillation is the cause. We ourselves observed such a case of sudden cardiac death in a subject with leptospiral infection while we were feeling the pulse. Shortly before the cardiac arrest it was very irregular. We lacked the opportunity of making a tracing of this irregularity. Microscopically the heart showed focal myocarditis. After this experience we gave patients with leptospiral infection, as soon as they showed extrasystoles, quinidine sulphate, and it would be probably right to do the same in other infectious diseases, when extrasystoles or fibrillation arise. In this connection, however, we must remark that the whole syndrome in the above infectious conditions, generally has a good prognosis.

Summary.

In one patient with leptospiral infection and three with pneumococcal pneumonia, supraventricular extrasystoles were seen to appear, followed by periods of auricular fibrillation. By electrocardiographic analysis of one case the fibrillation was found to begin only when the premature auricular impulses followed the preceding auricular contractions so rapidly, that they were blocked at the atrioventricular junction. These observations agree with the production of experimental ventricular fibrillation by one single induction discharge or auricular impulse in the bled frog heart immediately after the refractory period (De Boer). As there is a small chance of ventricular fibrillation arising in these infective diseases, it is probably advisable to give quinidine sulphate when extrasystoles or auricular fibrillation arise.

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Flimmers. 1923.

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Studien über die Vasodilatatorfunktion bei einem Fall von wahrscheinlicher Herdläsion in der Medulla oblongata.

Von

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(Bei der Redaktion am 21. Mai 1942 eingegangen).

Geschichtliches: Trotz umfangreicher Untersuchungen über die Dilatation der Hautgefäße ist unsere Kenntnis auf diesem Gebiet noch unsicher und in vielen Punkten sehr lückenhaft. — Schon 1876 hat Stricker bei Tierversuchen festgestellt, dass faradische Reizung der hinteren Wurzeln die Hautgefäße in dem entsprechenden Hautgebiet erweiterte, ein Effekt, welcher ausblieb, wenn der periphere Nerv vorher durchgeschnitten wurde. Diese Beobachtung ist dann durch zahlreiche Forscher bestätigt worden (Bayliss, 1901, u. a.). Foerster (1936) hat beim Menschen konstatiert, dass bei faradischer Reizung des peripheren Stumpfes durchgeschnittener hinterer Wurzeln die entstehende Hautröte ihrer Ausbreitung nach im wesentlichen mit dem Gebiet des entsprechenden Schmerzdermatoms zusammenfällt. Dass auch zentrale Dilatationsimpulse die Hinterwurzeln passieren, haben Bayliss (1902), Fofanov und Tschalussov (1913), Hinsey und Gasser (1922), Bishop und Mitarbeiter (1933) u. a. nachgewiesen. Ob Vasodilatation durch Impulse über die vorderen Wurzeln eintreten kann, dürfte noch nicht ganz entschieden sein (siehe Bayliss, 1902, Fofanov und Mitarbeiter, 1913). Wahrscheinlich kommen gleichzeitig mit den aktiven Vasodilatationsimpulsen durch die Hinterwurzeln hemmende Impulse durch die vorderen Wurzeln an die Vasokonstriktoren vor. Eine

lebhaft Erörterung hat sich darüber entsponnen, über welche Bahnen in den Hinterwurzeln die zentralen Dilatationsimpulse vermittelt werden. Bayliss (1901, 1902), welcher keine anderen Bahnen in den Hinterwurzeln als die afferenten, sensiblen mit trophischem Zentrum in den Spinalganglien kannte, glaubte feststellen zu können, dass die Dilatationsimpulse antidrom in den sensiblen Neuronen geleitet werden. Derselben Ansicht sind Langley (1923) und Lewis (1927). Der letztere stützt sich auf die dermalen Veränderungen bei Herpes zoster. Mit Recht weist O. Müller (1937) darauf hin, dass die Hautsymptome bei dieser Krankheit ebensogut die Folge einer Reizung anderer als sensibler Elemente in den Spinalganglien sein können. Ken Kuré und Mitarbeiter (1927/28) bestreiten entschieden das Vorhandensein einer antidromen Leitung und schreiben »spinalparasymphathischen« Elementen die Fortleitung der Dilatationsimpulse zu. Durch verfeinerte histologische Technik haben diese Forscher feinkalibrige, markhaltige, efferente Fasern in den Hinterwurzeln feststellen können, deren trophische Zentren in den Vorderhörnern sowie im Gebiet gegen die Basis der Hinterhörner liegen. Diese Beobachtungen sind u. a. von Gabel (1930) bestätigt worden. Nach Sheehan (zit. nach Foerster 1936) soll ein Teil dieser Fasern die Spinalganglien nicht umgeschaltet passieren, während Ranson und Wightman (1922) Umschaltungsbilder solcher Fasern in den Spinalganglien beobachtet haben. Hinsey und Gasser (1930) nehmen an, dass die Vasodilatation, hervorgerufen durch Reizung dorsaler Wurzeln, ganz und gar durch Nervenfasern vermittelt wird, welche für die C-Wellen im Aktionspotentialbild verantwortlich sind. Die Leitungsgeschwindigkeit in diesen Fasern betrug ungefähr 2 m je Sek. — Der Streit darüber, welche peripheren Nervenelemente als Vermittler zentraler Dilatationsimpulse zu betrachten sind, kann noch nicht als entschieden angesehen werden, wenn auch jetzt die meisten Forscher auf diesem Gebiet, namentlich weil es unwahrscheinlich erscheint, dass ein und dieselbe Nervenfasern Impulse in beiden Richtungen vermittelt, zu der Ansicht neigen, dass es besondere Dilatationsbahnen gibt, wobei man in erster Linie an das »spinalparasymphathische System« (Ken Kuré) denkt. — Über die zentrale Fortleitung von Dilatationsimpulsen wissen wir äusserst wenig. In der Medulla oblongata befindet sich ein Vasodilatationszentrum, und durch Wärmereizung der Regio

hypothalamica hat man bei Tierversuchen Erweiterung oberflächlich gelegener Gefäße hervorrufen können. Wie von diesen Regionen die Dilatationsimpulse im zentralen Nervensystem fortgeleitet werden, ist vollkommen unbekannt. Ein Gegenstück zur Vaso-konstriktorbahn im Rückenmark kennt man für vasodilatatorische Impulse nicht.

Wie aus dem Gesagten hervorgeht, wissen wir über die Fortleitung von Dilatationsimpulsen sowohl im zentralen als im peripheren Nervensystem ziemlich wenig.

Eigene Untersuchungen.

Der folgende Fall, welcher in der hiesigen Medizinischen Klinik behandelt wurde, dürfte für die Beantwortung der hier berührten Fragen von gewissem Interesse sein:

G. L., Geschäftsvorsteherin, 42 Jahre alt, behandelt in der Medizinischen Klinik 19. 10.—26. 11. 1941 unter der Diagnose *Encephalitis acuta*. Frühere Krankheiten sind in diesem Zusammenhang ohne Interesse. Am 14. 10. 1941 bekam die Patientin Schnupfen. Am 17. 10. begann sie Stechen unter dem linken Fuss und am linken Bein hinauf zu fühlen. Als sie sich am 18. 10. morgens wusch, bemerkte sie, dass sich das kalte Wasser am ganzen linken Bein und auch in der linken Leiste lau anfühlte. — Bei den Untersuchungen in der Med. Klinik am 19. 10. wurde Folgendes festgestellt: Allgemeinzustand nicht beeinträchtigt. Rachenschleimhaut leicht gerötet. Über der Herzspitze ein weiches, kurzes, systolisches Geräusch. Herzgrenzen: 10,5 cm + 3 cm. S. R.: 34 mm nach 1 Stunde. Im übrigen nichts von Interesse seitens der inneren Organe. *Nervenzustand*: Kranialnerven: o. B. Spinalnerven: Motilität o. B. Die Sensibilität gegen Schmerz- und Temperaturreiz unterhalb der Nabelebene auf der linken Seite total aufgehoben. (Die Sensation war immer dieselbe, nämlich lau, wenn der linke Fuss in Wasser getaucht wurde, gleichviel welche Temperatur dieses hatte, z. B. 10° C und 45° C). Die Berührungssensibilität war nur leicht herabgesetzt. Gesteigerte Kitzlichkeit beim Streichen der linken Fusssohle mit einem spitzen Gegenstand. Tiefe Sensibilität o. B. Sensibilität auf der rechten Seite ganz intakt. Funktionen des Kleinhirns und der basalen Ganglien o. B. Blasen- und Rektalfunktionen o. B. Reflexe: Die Pupillen reagieren möglicherweise etwas träge auf Licht (die linke vielleicht etwas weiter als die rechte). »Fremd- und Eigenreflexe« im übrigen o. B. Lumbalpunktion in liegender Stellung: Initialdruck 13 cm. Queckenstedt's Probe o. B. Freie respiratorische Bewegungen. Liquor: klar, farblos, Pandy: pos., Nonne: Spur, Zellen: 128 Mononukleäre, 10 Polynukleäre sowie 3 Rote auf 3.2 mm². W.R. neg. — W. R. (Blut) neg. — Am 20. 10. schwaches, aber deutliches Hornersches Syndrom auf der rechten Seite. — Auf Grund des Erkrankens mit katarrhalischen Erscheinungen, der erhöhten Blutsen-

kungsgeschwindigkeit und der Liquorbefunde stellte man die Diagnose: infektiöser, entzündlicher Prozess im zentralen Nervensystem, welcher die sensiblen Störungen und das Horner'sche Syndrom hervorgerufen hatte. Bei einem solchen Prozess muss man mit der Möglichkeit multipler Herde rechnen, aber andererseits könnte die Annahme eines einheitlichen Herdes sowohl die Sensibilitätsstörungen als das Horner'sche Syndrom erklären. Dieser Herd würde dann in der lateralen, die kaudalen Körperteile repräsentierenden Partie des Tractus spino-thalamicus in der rechten Hälfte der Medulla oblongata liegen und bis zur Peripherie derselben reichen, wo die Sympathicusfasern des rechten Auges verlaufen. — Anfang November begann das Gefühl im Rumpfgebiet und in den oberen Teilen des Oberschenkels bis zu gewissem Grade wiederzukehren. Seitdem schritt die Besserung der Sensibilität in distaler Richtung während der folgenden Zeit fort, so dass bei der Entlassung am 26. 11. die Sensibilität gegen Schmerz- und Kältereiz nur noch wenig herabgesetzt war, die gegen Wärmereiz dagegen etwas mehr (siehe auch Fig. 1—3). Gleichzeitig mit der Besserung traten zunehmende Parästhesien in den betroffenen Gebieten auf.

Da ein kleiner, begrenzter, rechtsseitiger Herd in der Medulla oblongata, wo die sensiblen Bahnen relativ für sich liegen, wahrscheinlich war, bestand auch verhältnismässig grosse Wahrscheinlichkeit, dass, wenn die Vasodilatatorbahn wirklich nicht aus sensiblen Leitungsbahnen, sondern aus besonderen Nervenelementen besteht, die vasodilatatorischen Bahnen verschont geblieben waren. Unter dieser Voraussetzung erschien es aussichtsreich, die Frage zu entscheiden, ob zentrale Impulse zu Erweiterung der Hautgefässe antidrom in sensiblen oder durch besondere vasodilatatorische Bahnen gehen.

Durch zahlreiche Tierversuche wissen wir, dass bei einer Erhöhung der Temperatur des Gehirns in seiner Gesamtheit oder gewisser wärmeregulatorisch besonders wichtiger Teile desselben, namentlich der Hypothalamusregion, Impulse zu Erweiterung oberflächlich gelegener Gefässe erteilt werden. Untersuchungen zu gleichem Zweck beim Menschen waren mir nicht bekannt. Ich machte indes einen Versuch, durch Kurzwellenbehandlung des Gehirns Dilatationsimpulse hervorzurufen. Dabei wurden die Elektroden zu beiden Seiten des Schädels der Patientin in der Weise angebracht, dass die Verbindungslinie zwischen den Mitten der Elektroden durch die Hypothalamusregion ging. Versuchsbedingungen im übrigen: Siemens Kurzwellenapparat, Wellenlänge 5.6 m, Elektrodengrösse 84 mm, maximale Wärmeerzeugung ohne unangenehme Wärmeempfindung im Elektrodenfeld. Die Dauer

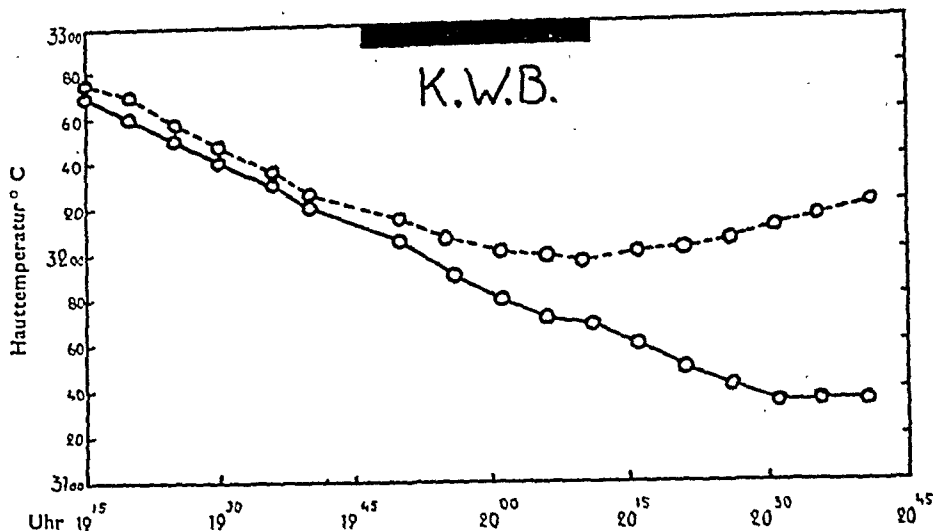


Fig. 1.

Versuchsperson: G. L., Fräulein, 42 Jahre alt. Versuch am 3. 11. 1941. Sensibilität auf der Aussenseite des linken Unterschenkels: gegen Berührung äusserst wenig herabgesetzt, gegen Schmerz- und Temperaturreiz ganz aufgehoben. Axillartemperatur vor K. W. B. 37.0°C , nach derselben 36.95°C .

K. W. B. = Kurzwellenbehandlung des Gehirns.

———— = Hauttemperatur auf der Aussenseite des linken Unterschenkels.

----- = Hauttemperatur auf der Aussenseite des rechten Unterschenkels.

der Behandlung betrug gewöhnlich 15—25 Minuten. Einmal musste die Behandlung vorzeitig abgebrochen werden, weil Schwindel auftrat. Als Indikator für die Reaktion der Hautgefässe wurde die Temperatur auf der Aussenseite der beiden Unterschenkel benutzt, welche mit dafür bestimmten Präzisionsthermometern gemessen wurde. Die axillartemperatur mass ich vor und nach der Kurzwellenbehandlung. Eine einheitliche Tendenz war dabei nicht zu konstatieren, und die beobachteten Veränderungen waren von einer kleineren Grössenordnung als bei den Hauttemperaturen. Insgesamt fanden 9 Versuche zu folgenden Zeiten statt, nämlich 1941: am 31. 10, 3. 11., 7. 11., 10. 11., 13. 11. und 24. 11. sowie 1942: am 2. 2., 9. 2. und 13. 2.¹

Bei der Untersuchung am 3. 11. 1941 (Fig. 1) bestand immer noch totale Anästhesie gegen Temperatur- und Schmerzreiz und eine leichte Herabsetzung des Berührungssinnes der Haut am linken Unterschenkel. Während die Hauttemperatur auf der gesun-

¹ Die Kurzwellenbehandlung war mit sehr intensiven Parästhesien im linken Bein verbunden. Im Anschluss an die Kurzwellenbehandlungen erfolgte immer eine sprunghafte Besserung der Sensibilität: „hatte ein weniger abgestorbenes Gefühl im Bein“.

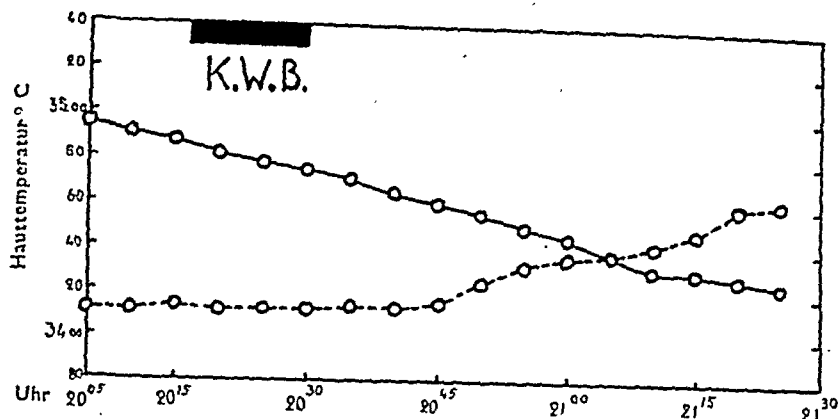


Fig. 2.

Versuchsperson: G. L. Versuch am 24. 11. 1941. Sensibilität auf der Aussen-
seite des linken Unterschenkels: gegen Berührung wie vorher, gegen Schmerz-
und Kältereiz leicht, gegen Wärmereiz etwas mehr herabgesetzt. Axillartem-
peratur vor K. W. B. 36.9° C, nach derselben 37.0° C. (Versuchsbedingungen im
übrigen und Figurbezeichnungen wie in Fig. 1.)

den Seite im Anschluss an die Kurzwellenbehandlung merklich
stieg, fehlte eine solche Tendenz auf der andern Seite ganz. Hieraus
kann man den Schluss ziehen, dass zentrale Dilatationsimpulse
durch Kurzwellenbehandlung des Gehirns ausgelöst wurden, und
dass solche Impulse nicht durch Berührungsbahnen vermittelt werden,
da der Berührungssinn bei dieser Gelegenheit so gut wie völlig
intakt war.¹

Bei dem in Fig. 2 dargestellten Versuch (am 24. 11. 1941) war
die Sensibilität gegen Schmerz und Kältereiz gut, jedoch etwas
schlechter als auf der rechten Seite, während das Wärmegefühl
noch immer etwas mehr gestört war. Trotz dieser Besserung der
Sensibilitätsverhältnisse trat keine Änderung der Reaktion gegen
die Kurzwellenbehandlung ein, woraus man schliessen kann, dass
auch die Bahnen für Schmerz- und Temperaturempfindungen von der

¹ Durch zahlreiche Untersuchungen sowohl an Tieren als an Menschen
konnte festgestellt werden, dass sich besonders bei stärkerer Wärmeeinwirkung
auf die Haut örtlich vasodilatatorische Stoffe bilden, die in den allgemeinen
Kreislauf übergehen (siehe Brenning, 1941). Natürlich ist anzunehmen, dass
sich bei der Kurzwellenbehandlung in unsern Versuchen eine gewisse Menge
solcher Stoffe im Elektrodenfeld gebildet hat, aber wegen der wenig intensiven
Behandlung nur in geringerem Grade. Es besteht doch kein Grund zu der An-
nahme, dass die Gefässe der beiden Seiten bei Direktapplikation solcher vaso-
dilatatorischer Stoffe verschieden reagieren und sich also die Gefässe der
anästhetischen Seite refraktär verhalten würden, weshalb auch die Ver-
schiedenheit in der Reaktionsart zwischen den beiden Seiten mit Sicherheit
als dadurch bedingt anzusehen sein dürfte, dass keine nervösen Dilatationsim-
pulse nach der linken Seite gelangt sind.

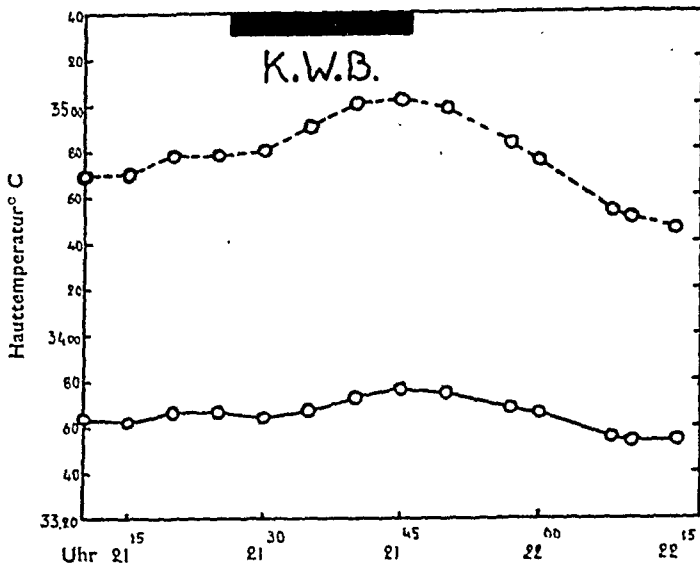


Fig. 3.

Versuchsperson: G. L. Versuch am 9. 2. 1942. Sensibilität auf der Aussenseite des linken Unterschenkels: gegen Berührung und Wärme wie vorher, gegen Schmerz- und Kältereiz möglicherweise etwas gebessert. Axillartemperatur vor K. W. B. 36.7° C, nach derselben 36.6° C. (Versuchsbedingungen im übrigen und Figurbezeichnungen wie in Fig. 1.)

Haut nicht die Unterlage zentraler Dilatationsimpulse sind, welche wärmeregulatorischen Zwecken dienen. Sämtliche während des Krankenhausaufenthalts vorgenommenen Versuche zeigten dieselbe Tendenz wie die hier mitgeteilten.

Gleichartige Versuche am 2. 2., 9. 2. sowie am 13. 2. 1942 ergaben, dass die Dilatatorbahn nach dem linken Bein in gewissem Umfang zu fungieren begonnen hatten. Aus Fig. 3 geht nämlich hervor, dass im Anschluss an die Kurzwellenbehandlung die Temperatur am linken Unterschenkel stieg, jedoch nicht so stark wie auf der andern Seite. Bei allen drei Versuchen wurde dasselbe Resultat erhalten. Die Sensibilitätsverhältnisse hatten sich seit der Entlassung aus dem Krankenhaus Ende November wenig verändert. Die Parästhesien waren weniger ausgesprochen, möglicherweise war die Sensibilität gegen Schmerz- und Kältereiz etwas besser geworden. Das Wärmegefühl hatte sich dagegen sicher nicht gebessert, was eine weitere Stütze dafür ist, dass die Bahnen des Wärmegefühls keine Dilatationsimpulse leiten, da ja seit November 1941 ein gewisses Leitungsvermögen der Dilatatorbahnen wiedergekehrt ist.

Die gemachten Beobachtungen zeigen deutlich, dass zentrale Dilatationsimpulse nach der Haut nicht längs Bahnen verlaufen.

welche Empfindungen der Haut vermitteln. Dies ist indes kein Beweis gegen die Theorie einer antidromen Leitung in den *peripheren* sensiblen Neuronen, da es denkbar ist, dass Dilatationsimpulse diesen auf anderen Bahnen im Rückenmark zugeleitet werden können als auf den Empfindungsbahnen.

Zusammenfassung.

Der Verfasser beschreibt einen Fall mit anfangs totaler Anästhesie gegen Schmerz- und Temperaturreiz sowie leichter Hypästhesie gegen Berührung der Haut unterhalb der Nabelebene auf der linken Seite, aber mit allmählich zurückgehenden Sensibilitätsstörungen. Auf Grund wiederholter vorgenommenen Messungen der Hauttemperaturen auf der Aussenseite der beiden Unterschenkel im Zusammenhang mit Kurzwellenbehandlung des Gehirns werden folgende Schlüsse gezogen:

1) Bei Erhöhung der Temperatur des Gehirns treten zentrale Dilatationsimpulse an die Gefäße der Haut auf.

2) Diese verlaufen nicht längs den Nervenbahnen, welche Impulse zu Schmerz-, Temperatur- oder Berührungsempfindungen in der Haut vermitteln.

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On chronic Thyroiditis, Riedel's Struma, »Hashimoto's Struma«, and Lymphadenoid goiter,

with Report of a Case of Chronic Thyroiditis.

By

KNUD LUNDBÆK.

(Submitted for publication June 5, 1942).

Classification of the diseases of the thyroid has always been rather troublesome. This applies not least to the group of affections that have been designated as chronic thyroiditis, Riedel's struma, Hashimoto's struma and lymphadenoid goiter. It is still a subject of discussion whether these forms of thyroid disease ought to be maintained as nosographic unities per se or whether two or more of them might be identical lesions. This uncertainty is probably due primarily to the relative infrequency of the affections making it rather difficult to collect a fairly large material of observations for comparison. Another confusing factor is the vagueness and variability with which these concepts often are defined, as a rule without paying any particular attention to the original descriptions.

In the following, a case of chronic thyroiditis will be reported, and the case history will be followed by a review of the literature relevant to the above-mentioned four pathological unities — in the hope that this may contribute to the nosographic elucidation of these unities and their mutual relation.

Case History.

The patient is a married woman, 41 years old with a negative family history as to disease of the thyroid. She gives a past history of good health, normal menstruation, one normal parturition 20 years ago and no abortion. She has had no climacteric symptoms. She has always been very obese, and her weight has remained unchanged through many years.

Present Illness. About half a year ago a swelling began to develop in the anterior aspect of the neck. It increased gradually in size and inconvenienced the patient by giving a sensation of pressure, and she «felt as if she had to swallow all the time». She was no longer able to lie on her back while sleeping. Apart from this, she had no complaints; in particular there were no symptoms of hyperthyroidism at any time; no fever or loss of weight. The other functions have been normal.

Physical Examination: Marked obesity (about 60 % overweight). She gives no impression of hyper- or hypothyroidism. The thyroid is moderately enlarged. This enlargement involves the entire gland, but the right lobe somewhat more than the left. The consistency of the thyroid is uniform, rather firm and hard, but far from the hardness of iron or wood. The surface is smooth and the skin is not adherent anywhere. On palpation the thyroid is slightly tender. No murmur. Circumference of the neck: 42 cm.

No other abnormalities revealed, especially not on examination of the skin, eyes and heart.

Various Examinations: Temperature normal (measured daily for 2 weeks). Urine: No pathological elements. Hemoglobin: 92 %. Red blood count: 4.45 million. Color index: 0.97. White blood count 9400. Icterus index: 5. Sedimentation rate: 12 mm/lhr. Differential count: Staff nuclear neutrophils 6.5 %; segment nuclears 62.5 %; eosinophils 0; basophils 0; monocytes 5.5 %; lymphocytes 25.5 %. Serum Ca: 10.7 mg %. Serum P: 3.94 mg %. Phosphatase: 59 Vermehren units. Wassermann negative. Basal metabolism: 95—99—98 %. Glucose tolerance test (1 g per kg): Fasting value 88 mg %, increased to 149 mg %, fall to fasting value in two hours. Hormonal analysis: < 30 R. U. of gonadotropin; < 20 M. U. of estrin. Electrocardiography: No abnormality. X-ray exam. of the trachea: Dislocation of the trachea to the right and slight compression. X-ray exam. of the heart, sella turcica and vertebral column: No abnormality.

Course and Treatment. For two months no treatment was given, in order to see if a spontaneous remission would take place. During this period, however, the goiter became somewhat harder, and the complaints persisted unchanged.

Biopsy (with a searcher) was performed on the goiter.

Histological Examination (F. 5059/41); [fig. 1].

The specimen shows an extraordinarily marked development of the stroma at the expense of the follicles. In many areas this stroma reminds of granulation tissue, with new-formation of tiny capillaries with intermediate accumulation of cells. A great many of these cells are plasma cells,

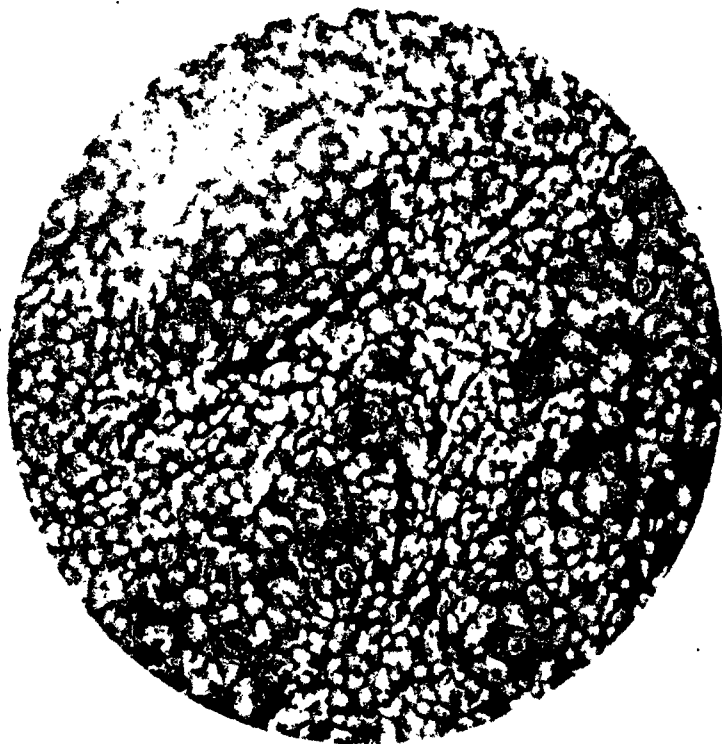


Fig. 1. Section from Biopsy of the thyroid.

which in some places stamp the picture in high degree; other cells are more or less mature lymphocytes, scattered reticulo cells and a few leucocytes. This loose tissue appears on the whole to be of inflammatory nature. In addition there are a few, rather coarse, streaks of connective tissue with plasma cells scattered here and there.

The follicles appear to be atrophic and are seen only here and there in the stroma, sometimes merely as small strands of epithelial cells, sometimes with distinct but small and irregular lumina, which contain no colloid but sometimes detached epithelial cells. In these places the epithelium is cuboidal, with rather large nuclei, here and there vesicular and irregular. In some places the cytoplasm of the cells has absorbed a good deal of eosin in the stain, undoubtedly a sign of degeneration.

Histological Diagnosis: *Chronic thyroiditis* («Riedel's struma, plasmocytic form»).

(Signed) Fridtjof Bang.

In keeping with previous experiences concerning diminution of chronic thyroiditis goiter after superficial surgical measures, no treatment was given during the following month in expectation of a possible remission. As the goiter kept unchanged, however, and the complaints persisted, X-ray

treatment was instituted $100\text{ r} \times 6$. Immediately after the X-ray treatment the goiter felt softer but the size was not diminished. Circumference of the neck 42 cm.

Three weeks after the X-ray treatment the patient was reexamined. Now the thyroid was barely palpable, and its consistency normal. Circumference of the neck 40 cm. The annoying sensation of pressure had disappeared completely and the patient was feeling well.

Various examinations: Hemoglobin: 76 %. Red blood count: 3.5 million. Color index: 1.03. White blood count: 2600. Sedimentation rate: 16 mm/1 hr. Differential count: Myelocytes 1 %; staff nuclear neutrophils 4 %; segment nuclears 64 %; eosinophils 1 %; basophils 0.5 %; monocytes 7 %; lymphocytes 22.5 %. Basal metabolism: 81—82 %. Glucose tolerance test: Fasting value 84 mg %, increased to 173 mg %, fall to fasting level in two hours.

Reexamination, 3 months after X-ray treatment: Feeling perfectly well. The thyroid appears normal. Basal metabolism: 103—93 %. Hemoglobin: 95 %; White blood count: 12,100. Differential count: normal. During the temporary decrease in metabolism the patient has gained 3 kg in weight.

Epicrisis: In a woman, aged 41, with a past history of good health, a hard non-toxic goiter developed that inconvenienced her merely by pressure symptoms. Ordinary physical examination revealed no abnormality except the goiter. X-ray examination showed a slight displacement and compression of the trachea. Laboratory examinations revealed no abnormality; in particular, the basal metabolism was found to be normal. Biopsy showed chronic thyroiditis. Her condition remained practically unchanged during two months' expectation.

After X-ray treatment the goiter and inconvenient symptoms disappeared. Now she is feeling perfectly well. The metabolism was temporarily lowered a little; now it is normal.

Discussion.

The case here reported shows the histological picture of chronic thyroiditis. As suggested already, however, it is identical with the condition which in the literature is often designated as the «plasmo-cytic form of Riedel's struma». Other authors have described a similar histological picture under the designation Hashimoto's struma or lymphadenoid goiter.

This fact naturally raises the question, which in recent years has been discussed ardently: the relation between chronic thyroi-

ditis and the peculiar rare conditions in the thyroid that have been designated as Riedel's struma, Hashimoto's struma and Williamson & Pearce's lymphadenoid goiter. This problem might seem to have been discussed sufficiently — from Denmark no less than 3 papers are published on this subject (Lund, 1935—36; Brændstrup, 1938; Hertz, 1940) — but on going through the accessible literature there appears to be good reason for trying to elucidate this rather intricate question.

At the present an ardent discussion is being carried on in American journals about whether Riedel's struma and Hashimoto's are identical. Most often Hashimoto's struma is identified with the lymphadenoid goiter originally described by Williamson & Pearce. Here an attempt will be made through a historical review to demonstrate: 1) that Riedel's struma is merely a macroscopic clinical picture that presumably most often covers the histological picture of chronic thyroiditis; 2) that the goiter described by Hashimoto is a histological picture that cannot be differentiated from that of chronic thyroiditis; and 3) that the lymphadenoid goiter originally described by Williamson & Pearce histologically differs from Hashimoto's struma — that is, from chronic thyroiditis — and that it is reasonable to maintain lymphadenoid goiter as a separate concept.

In a short paper read before the German Surgical Society in 1896, Riedel described 2 cases of »Chronische, zur Bildung eisenharter Tumoren führenden Entzündungen der Schilddrüse». In the course of 12 years, among 300 goiter operations, he had encountered two cases in which the struma was »eisenhart», so that it was suggestive of malignancy; it was operable only with great difficulty, owing to a peculiar ingrowth of the goiter in the surrounding tissue, in between muscles and blood vessels. The patients were inconvenienced merely by pressure symptoms. It is to be mentioned that with regard to the expression »eisenhart», he says himself that this perhaps was somewhat exaggerated. The histological description of sections from the specimens removed at the operation is very brief: »... zwischen normales Schilddrüsengewebe eingesprengt Anhäufungen von Rundzellen, wodurch jenes mehr oder weniger destruiert ist. Man ahnt bei der Betrachtung des Präparats nicht wie hart die Geschwulst ist; man erwartet derbes, fibröses Gewebe als Konstituens des Tumors, sieht aber, wie gesagt, lediglich eingelagerte Rundzellen.»

This report is illustrated by two drawings after sections. One shows a marked round-cell infiltration, the other appears to show a good deal of fibrous connective tissue; but the drawings are so poor that nothing definite may be said about them. It is to be noted that in this first description it is mentioned explicitly that no connective tissue proliferation was seen — especially because, later on, the chief importance appears to have been attached to the sclerosis. Next year, in 1897, Riedel demonstrated a new case of this kind before the same society. As to histological findings the report merely says that the specimen consists of »Spindel- und Rundzellen». In 1910 he again referred to the last-mentioned case but now he added »Auffallend ist die rasche Entwicklung von jungen bindegewebe.»

After this it is evident that the condition described by Riedel primarily is a *clinical* unity characterized by 1) a very hard goiter, 2) marked ingrowth of the goiter between the adjacent structures, and 3) a benign course. Histologically, the condition does not from Riedel's description appear as any well-characterized unity.

This morbid condition has to be looked upon as very rare, for many of the cases reported in the literature as Riedel's struma have not shown the characteristic ingrowth in the adjacent structures, and such an experienced goiter surgeon as de Quervain has evidently encountered only one case of this kind (de Quervain & Giordanengo, 1935—37).

In 1912 Hashimoto described 4 cases of »struma lymphomatosa». The patient had been inconvenienced by a hard struma for a few months. There were no symptoms of dysthyroidism, no fever. Histologically the specimens showed marked proliferation of the connective tissue that was studded with lymphocytes and plasma cells; in addition there were numerous »germ-centers». This picture was taken by Hashimoto as a disease *sui generis*, differing from Riedel's struma and chronic thyroiditis. As a differential diagnostic criterion with regard to chronic thyroiditis, the author stated that fever had always been absent in his cases, and histologically the specimens showed no giant-cells. As to differentiation from Riedel's struma he stated that in his cases the goiter was hard but not »eisenhart»; besides, »germ-centers» had not been described in Riedel's struma. Apart from this he found no histological difference between the two conditions. From Hashimoto's paper it is

evident that the author wanted primarily to set up the condition as a histological unity.

Thyroiditis has long been known as a concept, but only in the last generation has it been taken up for more thorough study. In 1895 Mygind described as the first the clinical picture of acute simple thyroiditis. In a larger work of 1904 de Quervain described a similar case and added hereto the histological picture of the lesion and a review of the literature concerning this disease. In his case it was an acute febrile disease with enlargement of the thyroid, pain and tenderness. Histologically he found epithelial desquamation, loss of colloid, polynuclear leucocytes, proliferation of the connective tissue, infiltration with lymphocytes and plasma cells, and less frequently »germ-centers». He further found some peculiar foreign body giant-cells round the remnants of colloid.

Chronic thyroiditis was first described thoroughly in the comprehensive studies by Reist (1922) and Simmonds (1923). Histologically these authors found infiltration with lymphocytes and plasma cells, occasional »germ-centers», besides proliferation of the connective tissue and degeneration of the glandular cells; in some cases also giant-cells.¹ Reist discusses the relation between chronic thyroiditis and Hashimoto's and Riedel's struma, emphasizing that there is no reason to differentiate Hashimoto's struma from chronic thyroiditis, as the most important criterion, the »germ-centers» indeed are present in many other cases in which the lesion undoubtedly has been chronic thyroiditis. Considering Hashimoto's cases and those described by Reist and by Simmonds, the only difference appears indeed to lie in the emphasis laid by Hashimoto on the finding of the »germ-centers». Actually the histological pictures described by these authors are alike. The same point of view is set up by Wegelin (1926). It is to be mentioned, too, that the clinical difference emphasized by Hashimoto — namely, that fever was absent in his cases — does not necessitate any differentiation of Hashimoto's struma from chronic thyroiditis, as the latter often takes a course without any elevation of the temperature (de Quervain & Giordano, 1935—37).

¹ Undoubtedly the preponderantly plasmocytic goiter described by Grünberg (1926) and by Hertz (1940) is to be reckoned as a form of chronic thyroiditis.

As to the differential diagnosis between chronic thyroiditis and Riedel's struma, Reist thinks there is no reason to maintain the latter as a disease *per se*, as it presumably always involves a pronounced degree of chronic thyroiditis. This view is further suggested by the fact that chronic thyroiditis presents various degrees of hardness, and that even the peculiar phenomenon, ingrowth into the surrounding tissues, is found also in ordinary thyroiditis though in a lesser degree (de Quervain & Giordanengo). In this connection, however, it is to be pointed out that presumably the clinical Riedel struma need not always be due to a chronic thyroiditis. This is suggested by a case reported by Brændstrup (1938). For about 1 ½ years this patient had showed signs of exophthalmic goiter, and then the struma became hard and immobile. Microscopic examination of the specimen showed a very marked proliferation of connective tissue but also signs of proliferation of the remaining parts of the glandular tissue of the same character as seen in exophthalmic goiter. In view of the histological studies reported by Bastenie (1934—35) on old «extinct» exophthalmic goiters, the features of which were quite the same as those observed by Brændstrup, it is reasonable to assume that in Brændstrup's case it has been such an «extinct» exophthalmic goiter that for some reason or other has developed into a very hard struma of Riedel's type. It seems justified, therefore, to maintain the concept «Riedel's struma» exclusively as a clinical designation of a very hard goiter with tendency to infiltrative growth between the adjacent structures and a benign course, independent of the histological character. This is the more reasonable as Riedel's original description of this condition was an entirely clinical account without any precise details of the histological features. Presumably a chronic inflammatory process is the underlying factor in *most* cases of Riedel's struma. A similar point of view was advanced by de Quervain & Giordanengo, (1935—37) even though these authors speak of a «Riedel struma in the stricter sense, the histological picture of which is not known in detail».

While thus the problem concerning Hashimoto's struma and, in part, Riedel's struma, too, appeared to have been elucidated, a new confusion arose when Ewing in 1928, in the 3' edition of his «Neoplastic Diseases», advanced the view that Hashimoto's struma and Riedel's struma really were two different stages of the same pathological unity *sui generis*. This assertion is repeated in the

subsequent editions of Ewing's work and appears to have been the cause of the standing controversy, especially in America, about the identity of the two concepts. According to the above, it seems unreasonable to discuss whether or not the conditions described by Hashimoto and Riedel represent the same lesion. As evidently the goiter described by Hashimoto and most instances of Riedel's struma probably involve a condition of chronic thyroiditis, the assertion that it may be a question of two phases of the same process does not really require any proof. The argument advanced, among others, by Ewing, that Hashimoto's struma may turn into Riedel's struma, seems obvious, but it by no means proves that every instance of chronic thyroiditis (*i. e.*, including Hashimoto's struma) terminates in the state resembling Riedel's struma.

When, nevertheless, this discussion is still kept up, it seems to be due to the peculiar fact that unnoticeably, in the course of time, the two concepts have been modified so that now they represent respectively a goiter with an intense lymphocyte infiltration and slight or no proliferation of connective tissue, and a goiter with marked proliferation of connective tissue but slight lymphocyte infiltration. This development of the concepts is connected with the peculiar fate which Hashimoto's struma has undergone, and the confusion resulting in particular from mingling his conditions with Williamson & Pearse's lymphadenoid goiter.

With exception of the cases briefly mentioned by Ewing in 1928, no new case of Hashimoto's struma was reported between 1912 and 1931. In 1929, however, Williamson & Pearse described a lymphadenoid goiter characterized exclusively by the marked accumulation of lymphocytes with suppression of the normal glandular tissue. No mention was made of »germ-centers». The authors thought that this condition terminated in a fibrosis of the type seen in Riedel's struma. In 1932 the same affection was described thoroughly by Joll in his comprehensive monograph on diseases of the thyroid, but he does not think that lymphadenoid goiter goes on to a fibrous Riedel-like struma. Neither Williamson & Pearse nor Joll mention Hashimoto's work, and it is obvious indeed that their histological pictures have differed essentially from the chronic thyroiditis described by Hashimoto with its combination of marked proliferation of connective tissue and lymphocytic infiltration.

In 1931 the first more recent descriptions were given of cases

diagnosed as Hashimoto's struma (Graham 1931; Graham & McCullagh 1931). In these cases, it is true, the histological features of the lesion appear to be identical with those described originally by Hashimoto. But Graham (1940) has since reported some additional cases of »Hashimoto's struma», among which there are both Hashimoto-resembling pictures (chronic thyroiditis) and cases of typical lymphadenoid goiter as described by Williamson & Pearse and by Joll.

Howard (1934), McClintock & Wright (1937), Hellwig (1938), Lehman (1940) employ the terms Hashimoto's struma and lymphadenoid goiter as synonymous designations of a histological picture with marked lymphocytic infiltration and »germ-centers», with slight or no connective tissue proliferation, *i. e.*, a picture resembling the one described originally by Williamson & Pearse, whereas it has nothing in common with the goiter described by Hashimoto.

Thus there appears actually to have arisen an entirely new histological unity characterized by an enormous accumulation of lymphocytes that almost completely suppresses the normal glandular tissue and has a tendency to form »germ-centers». It seems natural to designate this unity as »lymphadenoid goiter» — a term prevailing in the English literature — although the authors of this term, Williamson & Pearse, did not describe any »germ-centers» in their case. Whether this form of struma be identical with or related to Hashimoto's and Riedel's struma — *i. e.*, with chronic thyroiditis — can hardly be settled conclusively yet. Most of the arguments presented in the American literature apply to a variegated group of histological pictures and, as pointed out by Hertz (1940) they do not prove very much. For the present, however, it seems reasonable to maintain the lymphadenoid goiter as a special pathological unity as distinct from chronic thyroiditis.

For one thing, as mentioned, the histological picture differs in the two conditions. Chronic thyroiditis is characterized by proliferation of the cell-rich connective tissue, new-formation of capillaries, degeneration of the glandular tissue, accumulations of lymphocytes and plasma cells, with occasional »germ-centers» and occurrence of foreign body giant-cells, whereas lymphadenoid goiter shows an almost complete substitution of the normal tissue by lymphoid tissue with a tendency to the formation of »germ-centers» *without* any inflammatory features. Undoubtedly there

are atypical cases in which it may be difficult to decide whether one is dealing with one or the other of these pictures, but in most cases the particular character of the lymphadenoid goiter will be conspicuous. In his description of such a case de Quervain (1935—37) says that here »tritt der Ersatz des Schilddrüsengewebes durch lymphadenoides Gewebe, vielfach mit Keimzentren, derart in den Vordergrund, dass eine Verwechslung mit anderen Formen von chronischer Thyreoiditis kaum denkbar ist, selbst wenn dieselben verhältnissmässig reichlich Lymphozyten und selbst Lymphknoten enthalten sollten».

Furthermore, certain observations suggest the maintenance of lymphadenoid goiter as a concept *sui generis*. Hellwig (1938) has reported an instance of such a goiter that was treated surgically twice, at an interval of 9 years, and both times presented quite the same histological picture: marked lymphocytic infiltration with »germ-centers», and no connective tissue proliferation. Another observation, the significance of which is still obscure, is the case of clinical Addison's disease reported by Shaw & Smith (1925) in which the postmortem examination showed marked lymphocytic infiltration together with »germ-centers» in the thyroid and quite the same features in the suprarenals.

The nature of the pathological process in lymphadenoid goiter cannot yet be stated with certainty, but from the histological features it seems more likely to be a particular hyperplasia of the lymphoid tissue. The extensive studies reported by Simmonds (1911, 1913) on more than a thousand normal thyroid glands showed that scattered streaks and accumulations of lymphoid tissue occur normally in about 5 % of normal persons. In this respect the two sexes differ distinctly, the occurrence of the lymphoid tissue being about four times more frequent in women than in men. Strange to say, the frequency of this feature increases with the age, and in women over 30 years it is about 30 %.

Accordingly it seems reasonable to imagine that, in certain cases of persons whose thyroid contains lymphoid tissue, for some unknown reasons this tissue may undergo a marked hyperplasia leading on to the formation of the histological picture characteristic of lymphadenoid goiter. In keeping with this idea, indeed, lymphadenoid goiter appears to have been encountered only in middle-aged or old women (Joll, 1932).

Summary.

1. Description is given of a case of chronic thyroiditis. It is pointed out that such features as encountered here, often in the literature are designated as the »plasmocytic form of Riedel's struma», Hashimoto's struma or lymphadenoid goiter.

2. A historical account is given of the relation between Williamson & Pearse's lymphadenoid goiter, chronic thyroiditis, Hashimoto's struma and Riedel's struma. From this review it is evident that Riedel's struma is an entirely macroscopic-clinical concept: a very hard goiter with ingrowth into the adjacent structures and a benign course. Most often it is due to a chronic thyroiditis, but it may also occur in »extinct» exophthalmic goiter. The struma described by Hashimoto is essentially a histological unity that cannot be differentiated from the picture of chronic thyroiditis, and hence it seems unreasonable to maintain a special »Hashimoto struma». Nor can the »plasmocytic form of Riedel's struma» be differentiated from chronic thyroiditis.

3. The struma described by Hashimoto (chronic thyroiditis) is often confused with lymphadenoid goiter originally described by Williamson & Pearse. This is unjustifiable as from the histological picture of the affection and certain observations of such cases it seems natural to maintain the lymphadenoid goiter as a concept *sui generis*, distinct from that of chronic thyroiditis.

4. So the highly disputed question about the identity of Riedel's struma and Hashimoto's struma cannot be answered in the form in which it usually is raised. Riedel's struma and the goiter described by Hashimoto are identical insofar as they generally both involve chronic thyroiditis, but it is only in certain cases that chronic thyroiditis terminates in the entirely clinical picture described by Riedel. Lymphadenoid goiter which in the literature is often erroneously designated as »Hashimoto's goiter», is not identical with Riedel's struma, as it is no chronic thyroiditis.

5. The etiology and pathogenesis of lymphadenoid goiter are still obscure, but the writer finds it most likely to involve a hyperplasia of the lymphoid tissue present in the thyroid of some individuals, especially elderly women.

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Acute fatal kidney lesion in salvarsan-treated syphilitics.

(Obliterating Endarteritis of the Kidney.)

By

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The experimental studies which in the last 10—15 years have thrown some new light on the pathogenesis of arterial hypertension were largely carried out on animals by compression of the renal artery itself. From pathologic-anatomical studies we know that in sclerosis of the kidney and in the later stages of essential hypertension, the same effect — ischemia of the kidney parenchyma — is brought about by hyalinization and narrowing of the arterioles and glomerular capillaries. Between these two sizes of blood vessels the interlobar and arciform arteries occupy an intermediate position, but their rôle in this connection has attracted but relatively slight attention. Cases of periarteritis nodosa of these blood vessels have been described, in which the vascular lesion has been followed by hypertension; and these vessels may also be the site of arteriosclerosis as a part of a universal lesion of this kind. As far as we have been able to ascertain, however, solitary endarteritis obliterans of these arteries, accompanied by hypertension and with completely normal findings in the blood vessels proximal and distal to these arteries has been reported in the literature only once before [Leiter (14)].

In the following an account will be given of some cases of arterial hypertension with cerebral complications, in which the underlying renal ischemia was due to such an obliterating endarteritis. The etiology of this lesion cannot yet be looked upon as fully established, but from the evidence here presented it seems reasonable at present to reckon that the lesion is brought about by intensive salvarsan treatment of a relatively fresh syphilis.

Case Histories.

Case 1.

This patient (W. N.) was a workman, aged 36, who gave a past history of good health; in particular, he had never presented symptoms of any kidney lesion.

The date for his infection with syphilis is unknown, but Wassermann reaction in 1929 and 1936 was negative. In January 1939 an accidental Wassermann test gave a positive reaction: + 12. In April—June and in August—October 1939 the patient was under treatment in the Dermatological Dep. of the Rigshospital, where he was given neosalvarsan and bismuth in the usual doses. The last dose was followed by a pronounced salvarsan exanthema. In April—May 1940, therefore, the treatment was continued with mapharside and bismuth.

About January 1940 the patient felt tired and poorly and under the last series of treatment he often complained of headache, dizziness and insomnia. On 30/5—10 he had an epileptiform attack of convulsions in the street and was admitted to the Psychiatric Dep. of the Rigshospital, where he had several attacks of tonic-clonic convulsions during the following days. He was transferred to the Medical Dep. (B) of the Rigshospital, on 7/6, and here the convulsive attacks continued. He became increasingly drowsy, and universal small twitchings appeared, followed by a bilateral abducens paralysis; and the patient died on 27/6 with the clinical features of true uremia.

Of examinations performed in the various departments where the patient was under treatment, the following are to be mentioned:

Wassermann reaction, in April 1939: + 12; August 1939: + 8; April 1940: neg.; June 1940: + 1.

Urine, several analyses during the antisypilitic treatment in 1939 and 40, last in April 1940: No proteinuria. In the Psychiatric Dep. and, later, in the Medical Dep., the urine contained a large amount of albumin (Esbach: 2—11 ‰), several hyaline casts, but only an insignificant amount of blood (sedimentation count: 1.3—1.4 million red blood cells).

Blood urea: On admission, normal (20 mg %), and it stayed normal until shortly before death, when it rose to 296 mg %.

Blood pressure: On a single measuring, in June 1939 (*i. e.*, 1 year before

the onset of the present illness) the blood pressure was increased (170/80). On admission to the Psychiatric Dep. in 1940, the systolic pressure was 200—230, the diastolic 100—160, at which level it remained until death.

Lumbar puncture revealed an increased pressure, respectively 460 and 520 mm before evacuation of spinal fluid. The albumin and globulin values were normal; cell count: 2. Wassermann negative.

Eye examination on 1/6 showed no evidence of stasis but a slight haziness of the eyeground, small hemorrhages and thin arteries. On 8/6 there was bilateral choked disk (2 diopters) with small hemorrhages into the papillary tissue, besides amotion of the retina, temporally on the left side.

Blood examination, blood sugar determination, roentgenography of the heart, lungs, skull and bones, and hormonal analysis presented nothing of interest.

Intravenous pyelography: No excretion.

Treatment: The patient was treated with glucose, Carlsbad salt and morphine.

Autopsy showed scattered small hemorrhages in the brain, slight focal thickening of the intima of the aorta, and no other abnormalities outside the kidneys.

Examination of the kidneys, see below.

Case 2.

The patient (S. S.) was a workman, aged 27, who gave a past history of good health; in particular he had never had any symptoms of any kidney lesion.

In August 1940 the presence of syphilis was ascertained, and on 31/8—40 the patient presented remnants of a primary lesion, universal adenitis, papules on the genitals, in the scalp and in the mouth. He was under treatment in the Dermatologic Dep. of the Rigshospital in September—November 1940 and in March-June 1941, where he was given neosalvarsan and bismuth in the usual doses. The first serie of neosalvarsan as injections was followed by slight dermatitis.

About 1/8—41 the patient felt ill, complaining of tiredness, headache, nausea, vomiting and pain over the loins. On 2/9—41 he had a convulsive attack for which he was admitted to the Psychiatric Dep. of the Kommune-hospital, where, on the same day he had several attacks of tonic and clonic spasms. On 3/9 he was transferred to Dep. VII (medical) where he had several attacks of clonic spasms during the following days. He was drowsy and distant, with slight oedema of the face.

As the convulsions continued and the blood pressure kept increased, and as his condition looked desperate, on 7/9 he was transferred to Dep. I (surgical), where decapsulation of the kidneys was performed. The course of the operation was uncomplicated, but on the following day the patient was worse, with rising temperature and falling blood pressure, and he died one day after the operation.

In Dep. VII the patient was treated with venesection, glucose, lumbar puncture and morphine.

Neurological examination showed a positive Babinski on the right side, absence of patellar reflexes, but no other abnormalities.

Of special examinations the following are to be mentioned:

Wassermann reaction, 5/9—40: +12; 11/3—41 and 4/9—41: negative.

Urine: in August 1940 and March 1941, no albuminuria. 5/9—41: + albumin (Esbach 8 ‰). Microscopy, 5/9—40: A few granular and hyaline casts, besides a few red blood cells and some leucocytes.

Blood urea slightly increased (76—81 mg %).

Serum proteins showed a moderate decrease (6, 5.7 and 5 %).

Serum chlorine lowered (290 mg %).

Blood pressure: On admission, 210/160; later, 190/150.

Lumbar puncture, 5/9: Albumin 25, globulin 1, cell count 1, Wassermann negative; pressure before evacuation: 600 mm. On 6/9: Albumin 17, globulin 0, cell count 1.

Bicarbonate concentration, blood and spinal fluid sugar, hemoglobin percent and sedimentation rate: No abnormality.

Eye examination on 2/9 and 5/9 showed slight haziness and prominence of the papilla, normal arterial calibers, but greatly dilated veins, small hemorrhages, and considerable oedema of the retina.

Autopsy revealed oedema of the brain but no other definite macroscopic changes. Microscopic examination showed a slight perivascular accumulation of blood pigment in a few areas, but otherwise no pathological changes.

Examination of the kidneys, see below.

Case 3.

The patient (R. J.) was a butcher, aged 22 who gave a past history of good health except a hemorrhage from the kidneys, of brief duration, in 1937, which subsided spontaneously and was regarded as a sign of renal calculus.

In November 1940, the patient was infected with syphilis. In January-April 1941 he was treated with neosalvarsan and bismuth, and the bismuth treatment was repeated in July 1941. The first series of treatment was associated with an exanthema and was later followed by slight hepatitis.

In June 1941 the patient began to feel tired and poorly, complaining of headache on the left side. On 1/8 he had peripheral facial paralysis of the left side, for which he was admitted to the Neurol. Dep. of the Kommunehospital on 17/8.

Two days after his admission the patient had 2 attacks of tonic-clonic convulsions with complete loss of consciousness. Visual disturbances appeared at the same time, with dimness of vision which, in the next couple of days, developed into complete blindness. The patient stayed in the department about 2 months, during which time he presented varying degrees of oedema, increasing torpidity and debility, anemia, and ultimately extreme emaciation. Throughout this period he was completely blind. He died on 31/10 with the clinical features of uremia.

The patient was treated with repeated lumbar punctures, glucose, magnesium sulphate and morphine.

Neurological examination showed peripheral facial paralysis of the left side, loss of the sense of taste on the left half of the tongue, and positive Babinski on the right side.

Of special examinations the following are to be mentioned:

Wassermann reaction, January 1941: +8; August: negative.

Urine, in January, March and April: No albumin. On admission to Neurol. Dep. and throughout his stay here, the urine showed continuously content of protein, with a daily output of 5—12 %₁₀₀ (Esbach). Only slight hematuria (sediment count: 510000 red blood cells; 125000 leucocytes; 110000 hyaline casts).

Blood urea normal (24—50 mg %) until shortly before death, when it was rising.

Serum proteins between 5 and 6 %, on several examinations *i. e.*, a moderate decrease.

Serum chlorine lowered (265—287 mg %).

Blood pressure: In April 1941, normal; in the hospital it was constantly increased: systolic pressure, 175—225; diastolic, 100—160.

Lumbar puncture performed many times showed always an increased pressure, varying from 300 to 600 mm. On admission the albumin and globulin values were increased, 45/4, whereafter they fell off to 20/1. Cell counts normal. Wassermann negative.

Hemoglobin: On admission, 84 %; later falling off to about 50 %.

Blood sugar and spinal fluid sugar, blood counts and blood microscopy, spinal fluid urea and spinal fluid chlorine, ascorbic acid determination, prothrombin determination, bicarbonate determination and platelet counts showed nothing of interest.

Eye examination on 18/8 showed hazy borders of the papilla, slight oedema of the retina and a few hemorrhages. On 21/8: Very marked oedema of the retina with detachment below on the right side. In the following days, increasing detachment of the retina, in spite of compressing bandage; on 25/8, total detachment of the retina in both eyes.

Autopsy: Brain pale; meninges slightly opaque, especially over the anterior part of the brain. In the 4th ventricle, a few blood points on the right side, corresponding to the colliculus facialis. Microscopic examination: Slight subchronic leptomeningitis, in a few areas with beginning endothelial proliferation in the blood vessels, but no perivascular lymphocyte infiltration. In the parenchyma, a considerable degree of intercellular oedema throughout, separating the tissue elements so as to form numerous large and small meshes. Further, there is a diffuse glia proliferation with mostly progressive changes in the glia cells together with diffuse degeneration of the ganglion cells.

No changes in the blood vessels in the parenchyma.

The area round the facialis nucleus shows a few small and some larger diapedetic hemorrhages.

Heart somewhat enlarged, otherwise appearing normal.

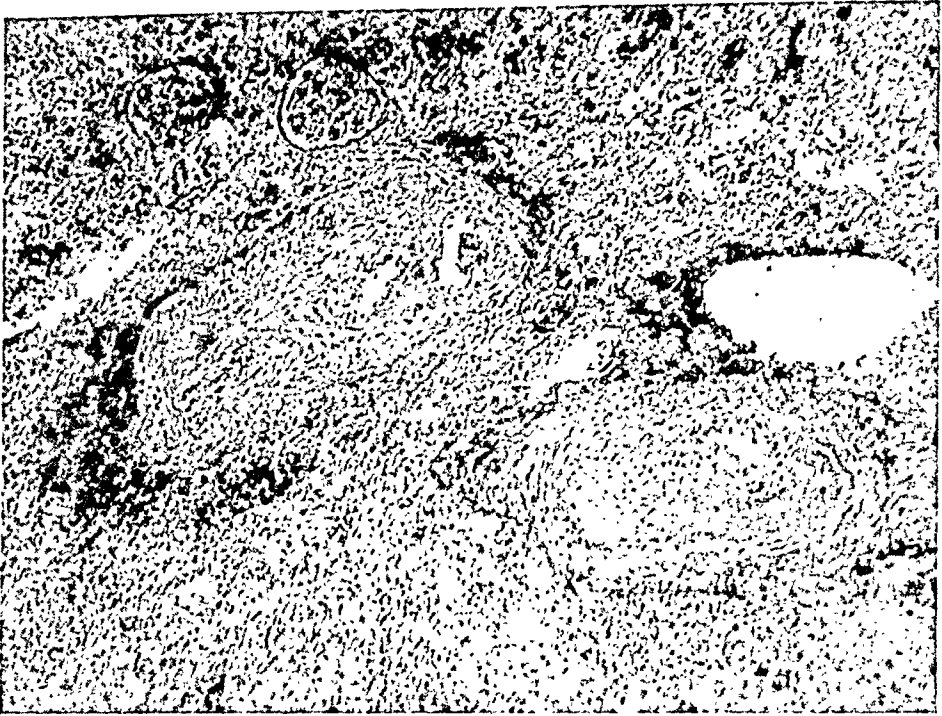


Fig. 1. Microphot. showing proliferation of intima and obliteration of the lumina of vessels of medium size (art. interlob and arciform.)



Fig. 2. Microphot. showing normal glomeruli and normal preglomerular vessels.



Fig. 3. Microphot. showing degeneration of tubular epithelium and atrophy of the parenchyma.

Microscopy of a lymph gland shows sinus catarrh and some endothelial proliferation in the blood vessels.

Examination of the kidneys, see below.

Kidneys. — The macroscopic appearance of the kidneys of the three patients is described almost completely alike by three examiners. The kidneys were about normal in size, marmorated on the surface with lighter, yellowish, slightly elevated areas that were sharply defined against the darker, depressed, more reddish areas. No macroscopic vascular changes.

The microscopic picture is dominated by pronounced vascular changes that involve exclusively the blood vessels of medium size: the interlobar and arciform arteries. These arteries are the site of a marked thickening of the intima, resulting in narrowing of the lumina producing here and there a complete obliteration and thrombus formation, but no perivascular infiltration with lymphocytes — *i. e.*, a typical endarteritis proliferans. (Fig. 1.)

A special feature in this picture is that the small blood vessels — the arterioles, interlobular arteries, vasa afferentia and glomerular capillaries — are completely normal, not hyalinized and constricted, as seen in every instance of primary and secondary renal atrophy (Fig. 2).

The glomeruli are perfectly normal, ruling out the possibility of a simple, acute glomerular nephritis, which would otherwise, *a priori*, seem most likely according to the clinical features of the cases. Likewise the possi-

bility of an acute exacerbation of a chronic glomerular nephritis may be regarded as excluded.

The tubular epithelia in all the specimens, especially in patient No. 3, showed degenerative changes resembling nephrosis. Finally, large parts of the kidney tissue have undergone shrinkage and atrophy from impairment of nutrition: (Fig. 3).

All the specimens, especially sections from Case 2, show scattered lymphocyte infiltration, but in no place does this present the character of the circular infiltrations described by Rich. (17) as typical of syphilitic kidneys.

Comments.

Presumably there can be no doubt that in these three cases we meet with a *nosographic entity*, as all the clinical and pathologic-anatomical features encountered here are perfectly identical.

All three patients were young men with a relatively fresh well-treated syphilis, and all of them had shown signs of intolerance for salvarsan. All three patients had been examined repeatedly with a view to affection of the kidneys but they never presented any subjective or objective signs of such a lesion (perhaps No. 3 is to be excepted, but the slight transitory hematuria in his case may be presumably left out of account in this connection); and during or after the antisymphilitic treatment, all three patients had uncharacteristic symptoms of nephritis, followed by accumulated epileptiform attacks of convulsions which gave rise to their hospitalization.

On admission to the hospital, all three patients presented pronounced hypertension, focal cerebral symptoms and increased spinal fluid pressure, which, in connection with the urinary findings and the eye changes, complete the clinical picture of an acute hypertensive encephalopathy on a nephritic basis. In all three cases there was marked albuminuria and tendency to oedema, but surprisingly slight hematuria. On admission there was no signs of renal insufficiency, but in two of the patients this phenomenon developed ultimately. All three patients died within 3 months of the first convulsive attack.

Autopsy revealed kidney lesions consisting in endarteritis obliterans of the larger blood vessels in the kidney with consecutive atrophic changes in the parenchyma and more or less pronounced nephrotic changes.

One cannot help wondering that it be possible within one year in hospitals of Copenhagen to encounter 3 patients presenting such striking clinical features and that it is impossible in the literature to find more than one case of the same kind — described in 1938 by Leiter (14). On the other hand, the patient of Leiter's falls completely in line with our patients. This patient was a male syphilitic, aged 40, treated with salvarsan and bismuth, who had hypertension and convulsive attacks, and died in the hospital. Like in our cases, the kidneys of this patient showed a typical endarteritis obliterans and thrombus formation in the interlobar and arciform arteries, but no abnormality of the small blood vessels and glomeruli. In this case the atrophy of the kidney tissue was more pronounced than in our patients, and the nephrosis-like features less conspicuous. Leiter thinks that his case is the only one of its kind described in the literature up to that time.

Undoubtedly the primary phenomenon in this morbid condition is the vascular lesion here described, giving rise to hypertension through narrowing of the kidney vessels and subsequent ischemia of the kidney tissue. Whether the nephrosis-like condition with pronounced albuminuria and oedema that makes its appearance later on is a result of this vascular lesion, or whether its production requires some additional factor, is a question that cannot now be decided with certainty. But, we know at any rate that the albuminuria has not persisted for any considerable length of time, and in one of our cases the hypertension was present about one year before the appearance of the albuminuria.

As to the *cerebral phenomena*, the reader is referred to a preceding paper in which this question is dealt with extensively (1).

The term «acute hypertensive encephalopathy» covers the concept of «acute eclamptic pseudo-uremia» — or, as it is commonly designated in the Scandinavian text-books «eclamptic uremia» — and is the designation for the cerebral phenomena accompanying certain kidney lesions, especially the acute glomerular nephritis, sometimes the chronic nephritis, less frequent nephrosclerosis, but never a clear-cut nephrosis. The typical morbid picture is encountered also in eclampsia in pregnancy and in encephalopathy from lead poisoning, appearing as epileptiform convulsive attacks and, some times, focal cerebral symptoms, possibly

eclamptic equivalents, mental disturbances, etc. The presence of hypertonia is required for the appearance of these attacks, probably also a tendency to oedema. On the other hand, in themselves the attacks have nothing to do with uremia, as typical cases (and this applied to our patients too) present no evidence of renal insufficiency — although, of course, the attacks may very well be coincident with uremia. The attacks are always accompanied by hypertonic neuroretinopathy, in which the examination reveals a narrowing of the arterial lumina in the background of the eye, oedema of the papilla and retina, »woolly» exsudates and sometimes detachment of the retina.

To enter into the pathogenesis of hypertensive encephalopathy would fall outside the scope of this paper, and it will suffice here to mention that the discussion of this question has been focussed especially on three theories. After the *first* theory the cerebral phenomena are interpreted as resulting from toxic parenchymal damage. Insofar as this implies an intoxication with known metabolic products, this theory is now discarded as the kidney function in the typical cases is unimpaired. According to the *second* theory, the eclamptic attacks and their equivalents are elicited by cerebral angiospasm [Oppenheimer & Fishberg (15), Evans (5), and others]. This theory is claimed to find support in the acute onset of the attacks, the transitory character of the symptoms and the observation of spasms of the retinal blood vessels during the attacks [e. g., Haselhorst & Mylius (7)].

Finally, the *third* theory explains the hypertensive encephalopathy as resulting from acute oedema of the brain [Traube (20), Zangenmeister (24), Blackfan (3), Volhard (21), Dereux (4), and many others]. Several facts are suggestive of the pathogenetic significance of the cerebral oedema: In the initial stage the clinical features correspond to the symptoms of increasing intracranial pressure. Further, the spinal fluid pressure is practically always increased, and the degree of choked disc encountered in this condition is too severe to be attributable to the local oedema of the retina alone. Moreover, the attacks may be provoked by administration of water [Rowntree (18)], while evacuation of spinal fluid and injection of hypertonic salt solution may check the attacks.

The theory which today encompasses the majority of viewpoints will be as follows: The hypertension elicits cerebral arterio-

spasms, which produce cerebral ischemia; the resulting parenchymal endothelial damage gives rise to an abnormal permeability of the capillaries, which again brings about oedema, increased intracranial pressure and universal anemia of the brain.

There are still many unsolved problems concerning this condition, however, especially the relation between the arterial hypertension and the cerebral angiospasm, and the significance of the eventual abnormal capillary permeability to the formation of oedema [Kessler and collaborators (12)]. For elucidation of these questions we are now engaged in studies on the hydrodynamic aspects of the spinal fluid in hypertonic and oedematous patients.

The diagnosis of the cerebral phenomena is found in practice to be rather difficult. In particular, in our cases the possibility of the presence of an *intracranial tumor* has been considered. This possibility was suggested by the subjective symptoms of increased intracranial pressure, the rapid development of choked disk and the convulsive attacks that were accompanied by focal cerebral symptoms. The arterial hypertension, the retinal lesion and the urinary findings are decisive of the diagnosis.

It seemed less probable that the condition in these cases might involve *uremic cerebral complications*, as there was no evidence of renal insufficiency, and the epileptiform convulsive attacks did not at all resemble the irregular muscular twitchings encountered in uremia.

The third possibility was that these attacks might be due to *cerebrospinal syphilis*. If so, the spinal fluid changes were most suggestive of syphilitic endarteritis, which not infrequently brings about epileptiform convulsions. But the possible presence of vascular changes of this nature would not explain the arterial hypertension, the retinal affection, and the increased intracranial pressure observed in our patients.

As to the *kidney lesion*, its resemblance to an ordinary glomerulonephritis is so great that the clinical picture offers no definite evidence to the fact that we are dealing here with a special form of kidney lesion. One wonders at the absence of hematuria and the rapid fatal course of the lesion, as these two features are uncommon in acute glomerulonephritis, but first the microscopic examination reveals conclusively that we are dealing here with something

else. Also the possibility of an acute exacerbation of a chronic nephritis would have to be taken into consideration, if the urine had not been examined repeatedly prior to the admission, when it had shown no abnormalities.

As is well known, vascular changes of the nature here described may appear in response to various noxious agents or from some cause that cannot be decided.

Our cases, we think, imply three possibilities with regard to this point.

It might be the question of an *essential thromboarteritis obliterans* — instances of Buerger's disease involving the kidneys. Pathologic-anatomically this disease cannot be differentiated from the changes observed in our cases, but we think that such an explanation would be rather unreasonable, as all the four cases described so far have been syphilitics presenting no symptoms of any vascular lesion in the extremities. Cases of Buerger's disease have been described, in which the lesion involved not only the extremities, but also internal organs and the brain. Thus, among others, Jäger (11) has described a case in which vascular changes were seen in the kidneys, too. But these changes were not limited to the larger arteries, but were found also in the arterioles and in the glomerular capillaries. So the localization of the vascular changes described by us appears not to be characteristic of Buerger's disease. Another and more probable possibility to be considered is the *syphilitic etiology*. As is well known, syphilis may give rise to the appearance of various kidney lesions: transitory albuminuria, the slight toxic proteinuria in the initial stage that subsides spontaneously or after institution of antisyphilitic treatment; the syphilitic nephrosis which occurs most often in the secondary stage and is sometimes characterized by excessively high values for output of albumin in the urine [Baker (2), Hermann & Marr (9)]. Such cases have been described, among other, by Patton & Corlette (16) in 1940, and in 1925 Warburg (23) demonstrated a patient who presumably was suffering from syphilitic nephrosis and thromboarteritis obliterans, but in his patient this lesion was localized to the extremities, not to the kidneys as in our patients, and there was no hypertension in Warburg's case.

As, in particular, mercury, but also salvarsan and bismuth, may give rise to similar nephrosis-like features, it has often been difficult to

decide whether the disease or its treatment was responsible for the kidney lesion. In such cases, only the course of the lesion after further treatment, or after discontinuance of the antisyphilitic treatment, may give the diagnosis.

As to the question about the specific etiology of acute glomerular nephritis and of the chronic nephritis sometimes observed in syphilis, opinions are divergent [Hein (8), Volhard (21), Baker (2)]. As mentioned, Rich (17) has described a presumably syphilitic kidney lesion with small round accumulations of lymphocytes in the parenchyma, but this appears not to have been recognized in general. On the whole, we think, it may be said that apart from the rare occurrence of gummata of the kidney there are no pathologic-anatomical changes in the kidneys that are specific of syphilis. The course of some kidney lesions, especially improvement under antisyphilitic treatment, however, may suggest that the etiology has been a spirochæta infection.

As to our cases, the clinical features are not in keeping with the syphilitic kidney lesions described hitherto. Our patients have been treated early and energetically, and the Wassermann reaction has become negative under the treatment, so that it does not seem reasonable to assume that a serious syphilitic affection of the kidneys has developed at the same time even though this possibility probably cannot be ruled out with certainty.

The third possibility is that the *neosalvarsan treatment* is the cause of the lesion. This is indicated primarily by the circumstance that our three patients had showed other signs of intolerance for salvarsan (nothing is known about Leiter's case in this respect). It is rather strange, however, that such a serious complication from salvarsan treatment should not have been described before. The complications mentioned in the literature as arising from this therapy are the fairly common shock-like phenomena after the injections and proteinuria, but not more severe damage to the kidneys [see Stoeckenius (19), however]. Furthermore dermatitis, hepatitis, and the so-called hemorrhagic encephalitis, may be seen. The clinical picture of the last-mentioned cases which have been described, among others, by Kühnel (13) has some resemblance to that of our cases — convulsive attacks and a rapid fatal course — but there is no hypertension or other evidence of renal affection. Further, the hemorrhagic encephalitis occurs most often in preg-

nant women, appearing immediately after injection of salvarsan, and it is generally interpreted as a Herxheimer reaction in the brain, which is found to be oedematous and show numerous punctate hemorrhages.

Of course, it is quite possible that some of the cases reported in the literature as instances of hemorrhagic encephalitis have actually been of the same nature as ours, since some of these reports fail to give information about the urinary findings, blood pressure, and microscopic examination of the kidneys. It is further to be kept in mind that the vascular lesion here described presumably sometimes develops in the course of a considerable length of time (in one of our patients, in one year) and that the patients then may be admitted to other clinics, so that the possible connection of the lesion with the salvarsan treatment may be overlooked.

Finally, indeed, there remains the possibility that salvarsan during the last couple of years — under the difficult conditions of manufacturing — may have changed in character and become more toxic, and that this is the reason why such cases have not been seen before. It has not been practicable to analyse the salvarsan preparations employed in our cases but in the period here concerned there has been no increase in the number of complications observed under antisypilitic treatment given in the Dermatological Department of the Rigshospital. On the other hand, an investigation carried out on the initiative of the *Medical Legal Council* in autumn 1940 — on account of two deaths after injection of salvarsan (apparently instances belonging to the hemorrhagic encephalitis group) — showed that the salvarsan employed in these cases was 50 % more toxic than permissible after the directions.

As the matter now stands, it is not practicable to decide why these three patients died, even though we find it most likely that death was due to the salvarsan treatment. At any rate, this possibility is so obvious, we think, as to urge the venerologists to employ blood pressure measuring, besides examination of the urine, extensively in patients complaining of headache, dizziness, vomiting, etc., during or after treatment with salvarsan, and to discontinue this treatment in the cases of relatively young persons showing hypertension.

It has been the purpose of this paper to call attention to a presumably rare and hitherto unrecognized kidney lesion that occurs

in well-treated syphilitics, and which has terminated fatally in all the cases described so far. At the same time, this lesion presents some particular pathologic-anatomical features which strikingly illustrate and confirm the experimental investigations which show that hypertension is produced not only by a narrowing of the smallest blood vessels in the kidneys but also by obstruction to the blood flow in the larger arteries of the kidney.

Summary.

Hypertension from renal affection is encountered generally in patients with pathological changes in the smallest arteries of the kidney, glomerulonephritis, nephrosclerosis. Further, it may result from obliterating lesions in the renal artery. Solitary vascular changes in the medium-sized arteries of the kidney (interlobar and arciform arteries) as the cause of kidney affection with hypertension have been described in the literature presumably but once.

Here a report is given of 3 cases of renal hypertension with cerebral complications (acute hypertensive encephalopathy) arising on the basis of obliterating endarteritis in the medium-sized arteries of the kidney.

The 3 case histories showed a striking harmony in the clinical course of the lesion as well as in the pathologic-anatomical changes. All 3 patients were fairly young men with a syphilitic infection of $\frac{3}{4}$ —3 years' standing who had been treated early with neosalvarsan and bismuth, and all of whom had showed signs of intolerance for salvarsan. In connection with this treatment there appeared a renal hypertension with albuminuria, but without hematuria. Subsequently, eclamptic phenomena developed together with increased intracranial pressure, hypertensional affection of the retina with choked disk and, in two of the cases, detachment of the retina. The patients died within 3 months after the first convulsive attack.

Histological examination of the brain showed oedema and small scattered hemorrhages.

Histological examination of the kidneys showed pronounced proliferation of the intima of the interlobar and arciform arteries, but no pathological changes in the arterioles and glomerular capillaries. The kidney parenchyma presented degenerative nephrotic changes and atrophic processes with lymphocytic reaction here and there.

The pathogenesis of hypertensive encephalopathy is discussed briefly. The kidney lesion might considerably be due to the following conditions:

- 1) essential thromboarteritis obliterans — Buerger's disease,
- 2) syphilis,
- 3) neosalvarsan medication.

The three possibilities are discussed, and the writers arrive at the conclusion that more likely the vascular changes in the kidney are to be looked upon as a reaction to the salvarsan treatment.

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Investigations into the Cause of the Physiological Hypoprothrombinemia in New-born Children.

II. Fat Digestion of New-born Infants¹.

By

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(Submitted for publication April 14th, 1942).

In order to study whether the cause of the physiological hypoprothrombinemia of new-born children might originate from a deficient digestion of fat and, hence, of the fat soluble vitamin K we have investigated, quantitatively as well as qualitatively, the fat content of the feces from a number of normal infants. The prothrombin content of the blood was determined on the 1st, 3rd, and 6th day of life.

Technique².

The feces was collected directly from the diaper as quickly as possible after defecation and was kept at about 0° C. All feces portions from the 2nd—3rd to the 4th—5th day of life were collected and analyzed together. The determination of dry matter is complicated by two sources of error, partly a contamination with urine and partly the drying-in in the diaper. The content of dry matter has been determined after drying to constant weight at 98° C. The

¹ This work has been supported by a grant from the Rockefeller Foundation.

² The feces analyses were carried out in the laboratory of the Health Commission, Copenhagen (Chief: E. Mejlbø).

determination of total fat, free fatty acids, soaps, and neutral fat was performed *ad modum* Holt, Courtney and Fale, as described by Uldall.

The prothrombin content of the blood was measured on capillary blood from the heel by means of a micro-modification of Quick's method (Plum and Larsen). The thromboplastin applied was the non-dried human brain preparation (Dam and Glavind) (normal value for adults by this method, 18—21 sec.)

Material.

The 21 children investigated were healthy, new-born infants and, except for one, they were born at full term; all of them were breast fed with addition of some sweetened water during the first days. All the children were born at the Department of Obstetrics B of the Rigshospital, Copenhagen¹, during the period from July to September 1941. The children selected had not been treated with vitamin K and their mothers had not received prophylactic vitamin K before delivery. Furthermore, the children were selected so that one half of them showed a decrease, and the other half an increase in the prothrombin content of the blood from the 1st to the 3rd day of life. No other selection of the material was made. As a basis of comparison, 11 older, normal, breast-fed infants were examined. The results may be seen from Tables 1 and 2.

Discussion.

When the results from the investigations of new-born children are compared with results obtained on older breast-fed infants, it may be seen that the dry matter content of the feces and the fat content of the dry matter are almost identical, the mean values being 25.7 and 23 per cent dry matter, and 33.1 and 36.1 per cent total fat, respectively. With regard to the composition of the fat, a somewhat lower content of split fats (free fatty acids + soaps) was found in new-born than in older breast-fed children, *viz.* 60.2 and 73 per cent, respectively. Moreover, the new-born children showed a greater variation in the values, as may be seen from Table 3.

¹ Our thanks are due to Professor E. Hauch, M. D., for the permission to examine the children.

If the relation between the prothrombin content of the blood and the fat content of the feces is investigated in the individual newborn children, it appears that no correlation between total fat and the prothrombin content of the blood can be found.

Table 1.

Fat analysis of the feces from 21 normal breast-fed infants, 2—5 days of age. The upper part of the table comprises children whose prothrombin content of the blood decreased between the 1st and 3rd day of life. The lower part of the table comprises values from children whose prothrombin content of the blood increased between the 1st and 3rd day of life.

Case Report Nr.	Birth weight	Feces				Prothrombin content of the blood					
		Dry matter in %	Total fat in % of dry matter	Free fatty acids and soaps in % of total fat (split fat)	Neutral fat in % of total fat (unsplit fat)	1st day		3rd day		6th day	
						Seconds	Per cent of normal	Seconds	Per cent of normal	Seconds	Per cent of normal
1117	3050	28	40.6	67	33	106	2.5	148	1.2	41	19
1129	4000	30	45.1	71	29	28	43	115	2	42	18
1125	1800	27	12.4	90	10	20	90	48	13	34	28
1115	3550	20	37.7	58	42	89	3.5	199	0.6	35	27
1227	3450	20	22.4	66	34	58	9	927	0.1	31	34
1221	2950	21	42.5	48	52	43	17	70	6	23	65
1191	3350	20	14.6	80	20	40	20	135	1.5	53	11
1189	2800	41	25.3	34	66	39	21	294	0.3	49	13
1187	2700	18	26.9	74	26	49	13	80	4.5	32	32
1199	2950	22	25.0	60	40	73	6	267	0.3	34	28
1195	2950	30	51.3	63	37	30	37	89	3.5	26	50
Average		25.2	31.2	64.4	35.5		23.7		3.0		29.6
1111	3450	25	22.2	70	30	55	10	37	23	34	28
1313	3900	25	16.8	13	87	369	0.2	141	1.3	89	3.5
1377	3450	25	13.5	51	49	510	0.1	88	3.5	36	24
1406	3300	30	49.0	57	43	136	1.6	98	3	39	21
1397	3350	23	57.0	90	10	177	0.8	82	4	37	23
1228	3350	23	28.0	22	78	77	5	80	4.5	45	15
1257	3150	34	40.0	56	44	77	5	57	9.5	47	14
1271	4150	21	29.8	44	56	556	0.1	279	0.3	64	7
1261	3700	26	36.0	85	15	51	11	35	27	57	9
1269	2850	30	58.5	66	34	160	1.0	79	4.5	46	15
Average		26.2	35.1	55.4	44.6		3.5		8.1		16.0
Total											
Average		25.7	33.1	60.2	39.8		14.1		5.4		23.1

Table 2.

Fat analysis of the feces from 11 normal breast-fed infants, 1 $\frac{1}{4}$ —7 $\frac{1}{4}$ months age.

Age in months	Sex	Weight	Feces			
			Dry matter in %	Total fat in % of dry matter	Free fatty acids and soaps in % of total fat (split fat)	Neutral fat in % of total fat (unsplit fat)
1 $\frac{1}{4}$	M	4200	21	28.0	70	30
2	F	3925	11	33.5	65	35
3	M	3700	31	38.0	70	30
3 $\frac{1}{4}$	F	5250	23	35.3	77	23
3 $\frac{1}{2}$	F	5200	29	64.5	71	29
3 $\frac{1}{2}$	M	5250	23	28.2	68	32
3 $\frac{3}{4}$	F	6050	37	41.1	88	12
4 $\frac{1}{4}$	F	7200	23	48.2	55	45
4 $\frac{1}{2}$	F	7000	18	22.9	84	16
7 $\frac{1}{4}$	M	6820	19	23.8	73	27
7 $\frac{1}{4}$	F	6910	20	34.0	83	17
Average			23	36.1	73.0	27.0

When comparing the groups of new-born children, the first group, in which the mean value of the prothrombin content of the blood increased from 3 to 29.6 per cent between the 3rd and 6th day of life, was found to contain a greater amount of split fat in the feces (64.6 per cent) than the second group (55.4 per cent), in which the mean value of the prothrombin content of the blood increased from 8.1 to 16 per cent. This result seems to indicate that the better splitting of fat must be brought in relation to the greater increase in prothrombin content of the blood.

Conclusion.

It has been shown that with respect to the fat content the feces from new-born children between the 2nd and 5th day of life does not differ from the feces from older infants. The content of split fat is, however, somewhat lower in new-born children than in older infants. Moreover, a certain correlation seems to exist between the content of split fat in the feces and the prothrombin content of the

Table 3.

Distribution of the material with regard to the content of split fat
(free fatty acids soaps).

Split fat in % of total fat	New-born			Older breast fed infants
	Children whose prothrombin content of the blood decreased from 1st—3rd day	Children whose prothrombin con- tent of the blood increased from 1st—3rd day	Total	
0—9.....				
10—19.....		1	1	
20—29.....		1	1	
30—39.....	1	0	1	
40—49.....	1	1	2	
50—59.....	1	3	4	1
60—69.....	4	1	5	2
70—79.....	2	1	3	5
80—89.....	1	1	2	3
90—99.....	1	1	2	0
Total	11	10	21	11

SPLIT FAT
IN FECES
PER CENT

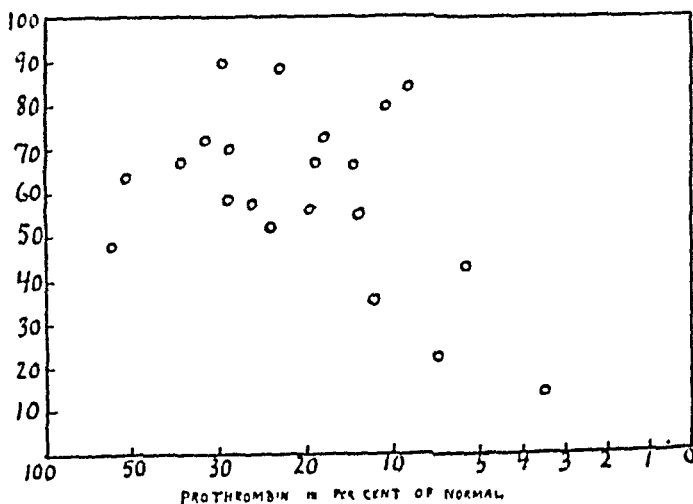


Figure.

Relation between the prothrombin content of the blood of the individual newborn children, measured on the 6th day of life, and the split fat content of the feces,

blood on the 6th day of life. Finally, the group of new-born children showing the greatest increase in prothrombin content of the blood between the 3rd and 6th day of life reveals a larger content of split fat than the group with a less pronounced increase in prothrombin content.

It being well-known that the absorption of the fat soluble vitamins A, D and K is closely connected with fat digestion (steatorrhea, bile obstruction) the circumstances demonstrated could be interpreted as an item in favour of the already quite probable assumption that new-born children's supply of vitamin K stands in relation to their ability to split and absorb fat. The greatly varying prothrombin values of new-born children might thus to some extent be caused by their fat digestion being at different stages of development. On the other hand, the differences demonstrated between the fat digestion of the new-born and older infants are so small that they cannot be considered to be the essential, but only a contributing cause of the physiological variations of prothrombin in new-born children.

Summary.

1. The dry matter content of the feces, the content of total fat and split fat (free fatty acids + soaps) have been investigated on 21 normal, new-born breast-fed children and 11 normal, older breast-fed infants.

2. The content of split fat was found to be somewhat lower in the new-born than in older infants. A doubtful correlation was found to exist between the content of split fat in the feces and the content of prothrombin in the blood.

3. The result of the investigations indicates that differences in the fat digestion and, hence, in the ability to absorb vitamin K play a contributing, but relatively small part as a cause of the physiologically highly varying prothrombin values of new-born children.

Literature.

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Some studies on blood coagulation, with reference specially to the problem of hemophilia.

By

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(Submitted for publication May 15, 1942).

The discovery of vitamin K and of heparin has greatly increased the interest of the clinicians in the subject of blood coagulation and has in many ways added to our understanding of this important process; yet many things about it are still speculative. The results of the investigations recorded in the following shed a new light on some aspects of the matter.

In the course of some studies respecting certain questions in connexion with the coagulation of blood I incidentally observed that citrated plasma underwent some changes when left standing. Thus, the fibrin coagulum obtained by addition of a lime salt gradually lost its power to retract when the plasma had been standing at a temperature of 37° C prior to coagulation, but at the same time the speed with which the plasma coagulated after recalcification increased.

The manner in which the retraction of the coagulum was examined need not be described here. The method by which the clotting time was determined was as follows. The principle is the same as in Howell and Gram's (7) method, in which citrated plasma is used, which is recalcified by the addition of calcium chloride. The blood is obtained by venipuncture, by means of a syringe, in the same manner as in Westergren's method for blood sedimentation, where-

by one part of a 3.7 per cent sodium citrate solution is added to four parts of blood; — this citrate concentration being preferred chiefly because it is practical for the prothrombin examinations, as will be mentioned later. When the blood corpuscles have sedimented, 0.2 cm³ of the plasma are set to heat at 37° C in a small test tube with an inside diameter of 10 mm. After a couple of minutes 0.05 cm³ of a calcium chloride solution are pipetted into the tube, care being taken to have this solution of exactly 1.5 per cent strength as regards CaCl₂, which has been found to give the best concentration for the coagulation. Thus, it is not necessary to investigate the clotting time with several different concentrations, but it must nevertheless be recommended always to make duplicate determinations. At intervals of 15 seconds the tube is tilted slightly in order to see if coagulation has set in, but in doing so care must be taken that the coagulum does not become detached from the wall of the tube. The clotting time, which thus is only determined with an exactitude of 15 seconds, will then be the time that elapses before the tube can be inverted without loss of the contents. Normally, the coagulation will occur after 3 to 4 minutes, but the limit for the pathological clotting must be set at 6 minutes. With plasma from normal subjects, the difference between the duplicate tests is hardly ever more than 1 minute.

The present investigations are based on the already mentioned observation that the clotting power of citrated plasma is greatly increased when it is allowed to stand for some time at 37° C, and in a lesser degree at room temperature. Of this, in my opinion highly interesting fact I have not found any mention in the literature to which I have had access so far, and I think it should be made the object of further study. What is particularly significant is that this acceleration of the coagulation can be demonstrated also as regards hemophilic plasma, as will be seen from Table I, where the clotting time for the latter is even shorter than in a control experiment with normal plasma. The experiment shows as clearly as anything that the hemophilic plasma contains a sufficient amount of clot-promoting substances, only, they are generally not present in an active form, either because one or several of the elements necessary to produce the coagulation are bound in some way or other, or because hemophilic blood contains a greater amount of clot-preventing substances (heparin, for instance) than normal blood. In

Table I.

Change in clotting time after standing.

Number of hours at 37° C.	Clotting time in minutes.		
	Hemophilia	Normal I	Normal II
0	10 $\frac{3}{4}$	2 $\frac{3}{4}$	6
1	8	2 $\frac{1}{2}$	5
2	3 $\frac{1}{4}$	1 $\frac{1}{4}$	2 $\frac{1}{2}$
3	2	1	—
4	1 $\frac{1}{2}$	1	2 $\frac{1}{2}$
6	2	1	2
21	36	1 $\frac{3}{4}$	3
at 21° C.			
0	10 $\frac{3}{4}$	2 $\frac{3}{4}$	6
3	8	2 $\frac{3}{4}$	—
21	4 $\frac{3}{4}$	2 $\frac{3}{4}$	3 $\frac{1}{4}$

this connexion it must be mentioned that it has already been observed that the clotting power of citrated plasma from hemophilic patients increases by standing [Opitz and Zweig (13)]; but this fact has not been paid sufficient attention to.

The hemophilic plasma was now centrifuged for 1 hour at 3500 r.p.m., and the supernatant plasma carefully pipetted off. The number of platelets prior to centrifuging was 370,000 per cubic millimeter, after centrifuging 1500. It was found that the centrifuged plasma did not coagulate until several hours after the centrifugation, and its clotting power was not increased by standing at 37° C.

Next, two portions of hemophilic plasma, each of 1 cm³, were centrifuged for 1 hour at 3500 r. p. m., and 0.8 cm³ of the supernatant, clear, almost platelet-free plasma pipetted off from each portion. One of the centrifuge cones, with the thrown-down platelets, and the plasma pipetted off from the other portion, were allowed to stand for 3 hours at 37° C. At the same time, two portions of untreated hemophilic plasma were set aside for the same length of time, one at 37° C, the other at room temperature (21° C), as controls. After the three hours, the plasma that had been pipetted off was again mixed with the corresponding platelet-containing plasma, and the mixtures shaken very carefully, so that the platelets became evenly distributed; whereupon samples were removed for determination of the clotting time. The results of this experiment, which was

Table II.

Observations on changes in plasma and platelets at 37° C.

	Clotting time, in minutes
Hemophilic plasma before standing	10 $\frac{3}{4}$
After standing for 3 hours, platelets at 37° C, plasma at 21° C	2 $\frac{1}{2}$
" " " " " platelets at 21° C, plasma at 37° C	10 $\frac{1}{4}$
After plasma with platelets standing for 3 hours at 37° C ..	2
" " " " " " " " " " 21° C ..	8

repeated several times, are shown in Tab. II. It is seen that where the platelets had been standing at 37° C and the corresponding plasma at room temperature, the clotting time is reduced considerably, whereas it does not alter in the cases where the platelets have been standing at room temperature and the plasma at 37° C. This shows with absolute certainty that it is the platelets that undergo a change when kept standing at 37° C, and which probably give off some substance that accelerates the clotting. The delayed coagulation of hemophilic blood must therefore in all probability be due to an abnormal reduction of the power to liberate this substance, which is presumably thrombokinase or some element present in the latter. This also accords with the theories emitted by several authors, respecting the cause of the disease. Fonio (5) and Minot and Lee (11), for instance, found that hemophilic plasma coagulates normally when a suspension of platelets from normal subjects is added to it. A significant, if somewhat coarse experiment was made by Birch (2), who separated platelets and plasma from hemophilic blood by centrifugation, crushed the platelets in a mortar and then added them to the plasma, whereupon the clotting time became considerably reduced.

The increased tendency to bleeding in hemophilia is presumably due chiefly to the prolonged clotting time, but some authors [Morawitz (12), Woehlich (17)] do not think that this is sufficient to explain the phenomenon, inasmuch as these patients often bleed without having sustained any demonstrable trauma. They therefore suggest the existence of an additional factor, namely some weakness, or brittleness, of the vessels; though no abnormality of the latter has ever been found in this disease, either by microscopy or by examinations of the capillary resistance. Moreover, it has been

shown that the amount of thrombokinase in the tissues is the same in hemophilia as in normal subjects [Gressot (8), Minot and Lee (11), Lowenburg and Rubenstone (10)].

As already said, it has also been suggested that the bleeding tendency in hemophilia should be due to an increased amount of anti-thrombin (heparin) in the blood, but this is very unlikely. In the first place it has been shown [Fonio (5), Morawitz (12)] that hemophilic blood does not inhibit the clotting of normal blood; in the second place, Eagle (3) has found that small quantities of thrombin will make hemophilic plasma clot just as rapidly as normal plasma.

On the other hand, a number of important studies by American workers on the problem of hemophilia indicate that the tendency to bleeding in this disease is due, not to an abnormality of the platelets, but to the plasma being deficient in an essential activating factor. In contrast to the investigators already mentioned, Eagle (3) found that the clotting of hemophilic plasma was not accelerated by the addition of a suspension of carefully washed hemophilic or normal platelets. Secondly, he found that the prothrombin content of hemophilic plasma was normal, and, thirdly, that the phospholipoid cephalin, which by many is considered as closely related to, or identical with thrombokinase, is ineffective when added to hemophilic plasma, despite the fact that it accelerates the clotting of normal plasma. These observations, which also agree with those of earlier workers [Addis (1), Frank and Hartmann (6), Feissly and Fried (4)], are contrary to the «platelet theory», and are furthermore supported by those of several later investigators, whose results point in the same direction. Thus, Patek and Stetson (14) found that the addition even of small amounts of normal plasma to hemophilic blood shortened the clotting time of the latter very considerably, irrespectively of whether the plasma used was untreated or had passed through a Berkefeld filter and was consequently free from platelets (Table III). The same was the case *in vivo*. Even an amount of normal or platelet-free plasma as small as 45 cm³ transfused into a patient with hemophilia reduced the clotting time from 120 minutes to 40, and with 300 cm³ of blood the time was reduced from 90 minutes to 10. Also these authors found that carefully washed platelets failed to accelerate the clotting of hemophilic blood, and they believe that the contrary results obtained by Fonio and Minot must have been due to the platelets not having been adequately rinsed of plasma, so that

Table III. (Patek and Stetson).

Observations on clotting time of hemophilic blood after adding normal and hemophilic plasma from another patient.

	Clotting time, in minutes	
	C's I	Case II
2 cm ³ control hemophilic blood.....	120	75
2 cm ³ control + 0.03 cm ³ whole normal plasma ..	28	25
2 cm ³ control + 0.03 cm ³ whole hemophilic plasma	120	75
2 cm ³ control + 0.03 cm ³ filtered normal plasma ..	28	25

some of the latter may possibly have adhered to their surfaces. In a later study, Patek and Taylor (15) have confirmed this «plasma theory», and have shown that the activating substance in the plasma is a globulin which can be extracted from the latter. As shown by Pohle and Taylor (16), this globulin can even be injected intravenously and intramuscularly into hemophilic subjects with the result that the clotting time is considerably reduced.

To find out whether these American observations could be made to tally with the investigations recorded in the present study it was necessary to make fresh experiments. In these I used a hemophilic plasma whose clotting time before the experiment was 20 minutes, and normal plasma with a clotting time of 3.5 minutes. Of both these plasmas, a part was removed for centrifugation for 1 hour at 3500 r. p. m., and portions both of the centrifuged and the not centrifuged hemophilic plasma were placed in water bath for three hours at 37° C. During this period there unfortunately (by stand at room temperature) occurred a change in the clotting time of the hemophilic blood, which became considerably shorter; but the results are nevertheless convincing. Thus, it will be seen from Table IV that centrifuged and non-centrifuged normal plasma are equally effective in hastening the clotting of the hemophilic blood. The addition of centrifuged hemophilic plasma had no accelerating effect, of course; but hemophilic plasma that had been standing for three hours at 37° C had this effect in a very marked degree.

The experiments were repeated in a still more convincing manner by the use of centrifuged hemophilic plasma with a clotting time of

Table IV.

Observations on the clotting time of hemophilic plasma after adding different types of plasma.

	Clotting time in minutes
0.2 cm ³ hemophilic plasma that had stood 3 hours at room temperature	8 ½
0.2 cm ³ normal plasma that had stood 3 hours at room temperature ..	1 ½
0.2 cm ³ hemophilic plasma + 0.02 cm ³ normal plasma	4 ½
0.2 cm ³ » » + 0.02 cm ³ normal, centrifuged plasma ..	4 ½
0.2 cm ³ » » + 0.02 cm ³ centrifuged hemophilic plasma	10
0.2 cm ³ » » that had stood 3 hours at 37° C	1 ¾
0.2 cm ³ » » + 0.02 cm ³ hemophilic plasma that had stood 3 hours at 37° C	2 ¾

several hours, in contrast to the centrifuged normal plasma, whose clotting time was 8 minutes and 45 seconds. (Clotting times of over 1 hour are in the present study called »infinite», because the clotting obtained after that length of time is very vaguely pronounced). As Table V shows, the clotting time for centrifuged hemophilic plasma does not change demonstrably by stand at 37° C. When normal plasma is added to it, the clotting is considerably hastened, as might be expected, and the same is the case if hemophilic plasma that has been standing at 37° C is added; but what is most significant is that hemophilic plasma that has been standing at 37° C and has then been centrifuged for one hour has a similar accelerating effect. On the other hand, the addition of hemophilic plasma that has first been centrifuged for one hour and has then been standing for three hours at 37° C does not demonstrably hasten the clotting. The results of these experiments most strongly indicate that the active, clot-promoting substance normally is present in the platelets, but can be liberated from there into the plasma.

As the clotting-power also of normal plasma is increased by stand both at 37° C and at room temperature, the explanation of the results of the experiments made by Patek and his collaborators with platelet-free plasma must probably be that the platelets had already given off the active substance to the plasma either before or during the Berkefeld filtration. Thus, they in some cases used plasma that was already four days old. That they, in contrast to other

Table V.

Observations on the clotting time of centrifuged hemophilic plasma after addition of different types of plasma.

	Clotting time in minutes
0.2 cm ³ centrifuged hemophilic plasma	infinite
0.2 cm ³ normal, centrifuged plasma	8 $\frac{3}{4}$
0.2 cm ³ hemophilic plasma, centrifuged and afterwards stood for 3 hours at 37° C	infinite
0.2 cm ³ centrifuged hemophilic plasma + 0.02 cm normal plasma ..	11 $\frac{3}{4}$
0.2 cm ³ " " " + 0.02 cm ³ hemophilic plasma that had stood 3 hours at 37° C	3 $\frac{1}{2}$
" " " + 0.02 cm ³ hemophilic plasma kept for 3 hours at 37° C and afterwards centrifuged	8 $\frac{1}{2}$
0.2 cm ³ " " " + 0.02 cm ³ hemophilic plasma centrifuged and afterwards stood for 3 hours at 37° C.....	infinite

investigators, did not find normal platelets available for enhancing the clotting of hemophilic plasma is probably because they washed their platelets so thoroughly that they became destroyed by the treatment. The fact is that — as we shall see later — the platelets give off the active substance so rapidly that it is almost impossible by centrifugation of normal blood to obtain a platelet-free plasma whose clotting time is essentially longer than that of the corresponding whole plasma.

In other words, the results of the experiments made by Patek and his coworkers can all be explained on the basis of the platelet theory. It must be admitted, though, that on first consideration it seems astonishing that, for instance, the addition of 1 volume of normal plasma to 100 volumes of hemophilic blood should be sufficient to cause so considerable a change in the clotting time. The explanation of this is not difficult, however; it lies in the fact that normal blood contains a large surplus of the substances on which the coagulation depends. A few examples will show this. In thrombopenia, for instance, the bleeding time will often not become protracted until the

number of platelets falls to 20 per cent of the normal, and even then there is no very noticeable change in the clotting time. In Fig. 1 will be seen a curve which shows the dependence of the clotting time on the number of platelets. (A series of plasma samples containing

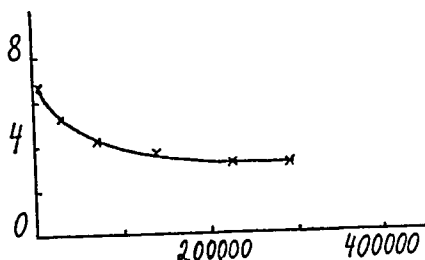


Fig. 1. Abcissa: Number of platelets per mm³.
Ordinate: Clotting time in minutes.

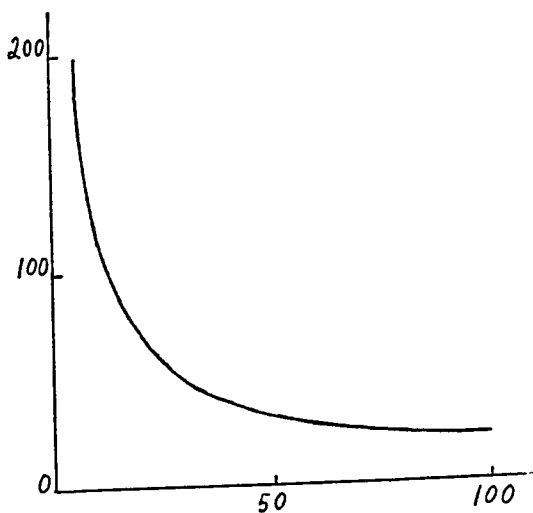


Fig. 2. Abcissa: Amount of prothrombin, in per cent of the normal.
Ordinate: Clotting time in seconds, by Lehmann's method for the determination of prothrombin content.

different numbers of these were obtained by centrifugation). Only when the platelets become very much reduced in number does the clotting time exceed the limit for the normal. Something similar is the case as regards prothrombin. In Fig. 2 will be seen a curve which shows the dependence of the clotting time on the amount of prothrombin in the plasma when a surplus of thrombokinase has been added (Prothrombin examination by Lehmann's method). A cor-

responding dependence of the clotting time on the addition of heparin will be seen from Fig. 3, which shows that the time level does not change in any marked degree until so great an amount of that substance has been added that the greater part of the clot-promoting substances have become neutralised; but when that has occurred even insignificant amounts of heparin suffice to delay the coagulation immensely.

In connexion with the question of hemophilia it will be reasonable to examine the dependence of the clotting time on the thrombo-

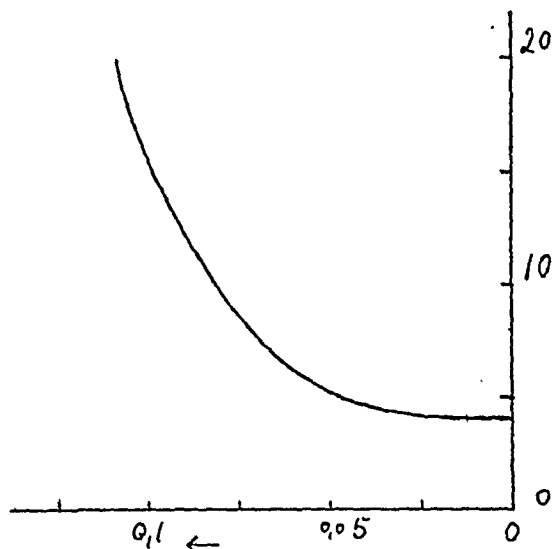


Fig. 3. Abscissa: Amount of heparin added, in per thousands.
Ordinate: Clotting time in minutes.

kinase. This is illustrated in Fig. 4. (The curve has kindly been furnished me by Mr. Hammer, Pharmacologist to the Biochemical Institute of the University of Aarhus). A plasma in which the prothrombin had been partly inactivated by heating was used for the experiment. Also here we see that minimal amounts of thrombokinase hasten the clotting time somewhat, when the latter is slow. There is, in other words, nothing surprising in the fact that 0.03 cm^3 of normal plasma will make 2 cm^3 of hemophilic blood coagulate with almost normal rapidity. That I in my experiments had to use comparatively more plasma is because I worked with a hemophilic plasma that had been standing for some time, and the clotting time of which had, in consequence, become rather short; whereas Patek and Stetson used fresh hemophilic blood. In principle, there is no difference between their experiments and my own.

The curves in Figs. 1—4 also show very clearly why blood transfusion has such good hemostatic effect in diseases with a tendency to bleeding. In hemophilia, the reduction of the clotting time lasts a couple of days, which corresponds with the supposed viability of the platelets (10).

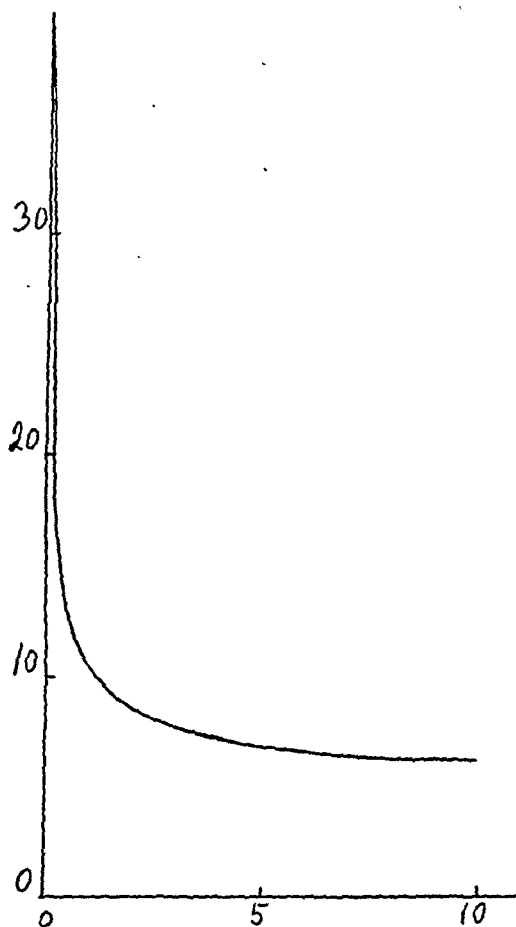


Fig. 4. Abscissa: Amount of tissue-thrombokinase added.
Ordinate: Clotting time in minutes.

To understand the hemophilia it is also important to know that there is no difference in the prothrombin contents of normal and hemophilic plasma. This has been shown by Eagle (3), and is confirmed by my own experiments. In these I used Lehmann's (9) modification of Quick's method, the principle of which consists in adding an excess of thrombokinase from brain tissue to citrated plasma and then recalcifying. The clotting time will then depend

mainly on the content of prothrombin. That thrombokinase will make hemophilic blood coagulate as rapidly as normal blood is very interesting, because it shows that the substance lacking from the blood in this disease is present in the thrombokinase. It has been believed that cephalin was identical with thrombokinase, but this is unlikely, because Eagle's investigations show that whereas cephalin shortens the coagulation time of normal blood it is unexplainedly ineffective when added to hemophilic plasma. The cephalin must therefore supposed to be only one factor of the thrombokinase, while the other substance is perhaps precisely the same as Patek's »globulin», which in my opinion derives from the platelets.

Summary.

The investigations related by the author are based on the observation that citrated plasma will coagulate more rapidly after recalcification if it has first been left standing for some time at 37° C.

The same is the case with hemophilic plasma, which after standing for 3 hours at 37° C can be made to coagulate just as rapidly as normal plasma; which shows that hemophilic blood in reality contains a sufficient quantity of the substance necessary for the occurrence of normal coagulation. The author shows that this increase in the coagulability of the hemophilic plasma is due to the fact that substances hastening the clotting become liberated from the platelets into the plasma.

The results of these experiments make it probable that the long clotting time in hemophilia is due to deficient power of the platelets to give off these substances, which are presumably a part of the thrombokinase complex.

The apparatus used in carrying out the present investigation were placed at my disposal through the kindness of the »Miss P. A. Brandt Endowment Fund», for which I express my grateful thanks.

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Types of pneumococci in pneumococcal affections of adults in Holland.

By

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(Submitted for publication May 7, 1942).

In 1938 we gave a report of preliminary investigations on the type-distribution of pneumococcus-strains in pneumococcal infections in adults (March, 1935—February, 1938) (1). As these investigations concerned only a small number of patients, we have continued them up to September, 1940.¹

For the value of our results it is important that we could personally follow the clinical course of the cases in Groningen. This probably contributed to keep the number of errors in the determination of types rather low, as we ourselves could always take into consideration and judge of the clinical significance of the types found, and the nature of the sputum (pharyngeal or pulmonary). Of the greater part of the cases from Amsterdam we were sent the clinical data.

The diagnostic sera we used were sent to us by the Lederle Laboratories, New York and from the Robert Koch Institute, Berlin.

¹ We are much indebted to Prof. Dr. J. G. G. Borst, who during the last two years regularly provided us with material for typing from the Binnengasthuis at Amsterdam. The figures finally resulting mainly represent the distribution of cases from the town and province of Groningen and from Amsterdam.

Remarks on the technique of pneumococcus-typing in sputa and pus.

Increasing experience in pneumococcus-typing has taught us the following:

1. The Neufeld method is indispensable, especially in material sent from elsewhere, in which sputum and saliva are often thoroughly mixed up, and cleaning of the flakes by washing is difficult. We did not find this procedure give inferior results in forwarded sputa as compared with those obtained in sputa collected at the place of examination and immediately worked up. We only found sometimes the forwarded material not to be lung sputum at all, but pharyngeal mucus (Gram-staining).

Every sputum must be kept in the ice-chest, in order to allow of making a control preparation by the Neufeld method after the type has been determined by culture or mouse-inoculation.

2. The technique of immediate inoculation of well-washed sputumflakes in serum broth, in order to obtain rapidly a selective growth of pneumococci, has been practised to our great satisfaction. We only often found type III not to grow as well on first inoculation in serum-broth as on the blood-agar plate.

3. Of forwarded samples a mouse-inoculation must be done, when the type cannot be immediately determined by the Neufeld method, as one cannot easily obtain another supply of the sputum from elsewhere in case the culture fails.

4. The type-determination in a culture by means of slide-agglutination with mixed test sera sometimes gives difficulties, as some sera do not keep a sufficient titre after dilution with three or four other sera. This also holds for the capsular swelling, but in most of the cases very satisfactory swelling is obtained with mixed sera.

5. A type diagnosis may only be based on the production of capsular swelling, as agglutination with undiluted sera is not always specific. Kaufmann (2) recently has analysed a great number of strains closely related to the Cooper types. His work had not been published at the time of our investigations.

6. Capsular swelling often fails to produce itself when large amounts of pneumococci are taken from a culture, so that this phenomenon must be looked for with only a few organisms on the slide.

The mixed sera in use were composed as follows, taking in view the distribution of types we had found in this country: (I) — (II, III) — (4, 5, 7) — (6, 8, 9, 12) — (10, 11, 13, 16) — (14, 15, 18, 19) — (17, 20, 21, 22) — (23, 24, 25, 27) — (28, 29, 31, 32).

Type 5. The capsule of type 5 is often very narrow. This makes the picture with mixed sera often indistinct. With none of the types we had so much trouble in determining them as with type 5. This holds both for the American and Berlin sera.

Type 19. Of this type a number of variants was found with a serum provided for us by the Robert Koch institute Berlin (there called type »33« — serum). F. Kaufmann from the state serum institute Copenhagen on account of an absorbtive-test stated one of these variants being probably identical with his newly described type 19A.

Growth with β -haemolysis. This is very distinct in some strains, and especially frequent in type 5. We further saw it once very intensely in type 7 in a blood-culture, which at first led to an erroneous diagnosis of haemolytic streptococci. In type I, too, we once observed it.

Mixed infections. These always cause much trouble to the examiner. How much care is generally required in examining sputum for pneumococci, is illustrated by the following case from the Binengasthuis at Amsterdam:

Male, age 22. Pneumonia in right lower lobe. No blood-culture. The Neufeld preparation gave type II, as did the culture on blood-agar plate and in serum-broth. In the Neufeld preparation with type II serum however, we also saw some individual cocci without capsular swelling. A mouse, injected with sputum mixed with anti-II serum, died of sepsis by pneumococcus type I. The types I and II, therefore, were both present in the sputum. It is therefore that in routine practise it is better not to mix type I-serum, as being the most important one, with serum of type II and III.

It goes without saying that such mixed infections can easily be overlooked in routine practice. Gundel even supposes that lobar pneumonia is exclusively caused by the types I, II and III, and that the finding of higher types in this disease should be the result of faulty technique, by which the first-mentioned types should have been overlooked (3). We can only partially sustain this opinion, and are convinced of the possibility of the types 4, 5, 7, 8, 9 and 12 causing real lobar pneumonia. The types, 5, 7 and 9 we also found in the blood of pneumonia patients.

Table 1.

Distribution of the pneumococcal types in Holland (adults) (March 1935—Sept. 1940).

Types	Primary lobar pneumonia	Empyema	Secondary lobar pneumonia	Broncho- pneumonia	Purulent bronchitis (acute and chronic)	Meningitis	Peritonitis
I	137 ¹⁰	38	7	—	—	10	4
II	32 ¹	5	3	6 ¹	1	—	—
III	27 ⁶	3	7	10 ²	13 ⁵	4	—
4	8 ¹	—	—	3 ¹	—	2	—
5	16 ¹	3	3 ¹	—	—	1	—
6	—	—	2	3	10 ⁴	3	1
7	26 ¹	2	2 ¹	4	3	2	—
8	3	—	2	4 ¹	9 ¹	—	—
9	4 ¹	—	—	2	3 ¹	—	—
10	—	—	1	1	6 ²	—	—
11	—	—	—	1 ¹	2	1	—
12	3	—	1	—	—	2	—
13	—	—	—	1	2	—	—
14	1	—	—	—	1 ¹	—	—
15	—	—	—	4	—	—	—
16	1 ¹	—	—	2	2	—	—
17	—	—	—	2	6 ³	—	—
18	—	—	1	4	5 ¹	4	—
19*	4 ³	—	1	2 ¹	12 ²	3	—
20	—	—	—	2	—	—	1
21	—	—	—	2 ¹	4	1	—
22	—	—	—	—	5	2	—
23	1 ¹	—	—	3	5 ¹	1	—
24	—	—	—	—	2	—	—
25	—	—	—	—	—	—	—
27	—	—	—	—	—	—	—
28	1 ¹	—	—	—	—	—	—
29	1 ¹	—	—	2	—	—	—
31	—	—	—	3	2	—	—
32	—	—	—	—	—	—	—
unknown	2 ²	—	—	7	6 ¹	2	—

The small figures to the right above the numbers denote the number of finding of two types simultaneously.

* Including serological variants (probably mostly type 19 A of Kaufmann).

Table 2.

Distribution of the pneumococcal types in pct. in various pneumococcal affections in adults (March 1935—Sept. 1940 Holland).

Diagnosis	No. of cases	Pneumococcal types in pct.										
		I	II	III	4	5	6	7	8—32			
									8	9	12	14
Lobar pneumonia and empyema	304	58.5	12.0	90.	2.5	6.5	0	9.5	1.0	1.0	1.0	0.3
Broncho-pneumonia	64	0	10.0	16.0	5.0	0	5.0	6.5	57.5			
Bronchitis group	79	0	1.5	16.0	0	0	13.0	3.5	66.0			
Meningitis	38	26.5	0	10.5	5.0	3.0	8.0	5.0	42.0			

The distribution of types in the various pneumococcal affections in adults.

The tables 1 and 2 give the findings collected from March, 1935 till September, 1940. The number of findings of two types in the same patient is indicated in table 1 by a small figure to the right above the figure indicating the number of cases of the type. The types of Cooper are indicated by common numerals, the first three by Roman.

Primary lobar pneumonia. The great importance of type I in causing this condition is impressive. The higher types of Cooper (from 16 upwards) were mixed infections in the presence of types I, III, 5 and 7, with the probable exception of a case caused by type 19.

Empyema. The greater virulence of type I is also obvious from the large number of empyemas caused by this type. The higher types of Cooper (above type 7) have no practical importance in the causation of empyema in adults.

Secondary pneumonia. Influenzal pneumonias of 1939. Nearly all cases of this group were secondary pneumonias in influenza, arising during the epidemic of February-March, 1939. Most of them were observed at Amsterdam. In a small number of cases, in whom investigations were made to that purpose, high

Table 3.

Distribution of pneumococcal types in cases of otitis media and mastoiditis (0—20 years old) (B. W. L. Siemens).

Disease	No. of Cases	Pneumococcal types (No.)														
		I	II	III	4	5	6	7	8	14	17	19*	20	23	27?	
Acute otitis and mastoiditis (0—20 years old)	130	18 (14 pct)	2 (46 pct)	60 (46 pct)	7	5	3	3	1	4	1	18 (14 pct)	1	3	1	

* and variants.

complement-fixation titres and high mouse-protective values were found in the serum against the influenza-virus strain WS, so that it can be taken for certain that in Amsterdam — as was the case at Groningen — at the time an epidemic of respiratory virus-influenza prevailed.

Of great importance is the fact that in an influenza epidemic, too, the more virulent pneumococcal types prevail in pneumococcal affections of the lungs. Apparently the carriers of these types run a greater risk of getting commensal infections secondary to their influenza, than the carriers of the less virulent higher numbered types of Cooper.

Bronchopneumonia. A diagnosis as exact as possible of bronchopneumonia or focal pneumonia was aimed at. Forms merging into lobar pneumonia («confluent» bronchopneumonia) were sometimes observed. Type I does not occur in this group; type II was occasionally seen in typical focal pneumonia, as was type III. The higher types were frequently found.

Purulent bronchitis (acute and chronic). Type I is absent. The higher types prevail in number especially type 19 (including variants). Their parasitic nature is far from being established. Pure cultures are rare.

Meningitis. Type I prevails in number. Higher types are often found, among whom type III and 18 are the most important.

Peritonitis. Type I takes the main place.

Otitis media. A recent extensive study of the bacteriology of acute purulent otitis and mastoiditis was made by Siemens in the

Oto-laryngological Hospital at Groningen. (4) Among 300 strains he found 130 times pneumococci (43 pcl), 163 times haemolytic streptococci (54 %) and 8 times haemophilus influenzae (3 pcl).

The distribution of the pneumococcal types among his cases is given in table 3. The high frequency of type III in otitis is a long-known fact that remains of much interest. Of further interest is the frequency of the type 19 (inclusive variants) which is especially found at very early ages. It is also important that the type-distribution in otitis and in purulent meningitis do not run parallel as to type III.

Indefinable types. Among the 560 strains, 17 (3 pcl) could not be defined. The types 25, 27 and 32 were not met with among our 560 strains (Siemens once found type 27).

The type distribution we found in pneumonia and empyema of adults agrees with the findings of Bullowa in New York (3389 cases). (5) He found type II in 8.5 % of his cases. In America the types 8 and 14 are of more importance than in Holland.

As newly we received the diagnostic sera of the types 33, 34, 35, 36, 37 and 38, established by Kaufmann, the number of undefinable types may in future be reduced.

The importance of typing pneumococci. Before the introduction of chemotherapy with sulfapyridine, typing was of much use for the rapid application of specific antiserum. Serum therapy is now only indicated in severe septic cases of pneumonia, in cases which don't respond to sulfapyridine or sulfathiazole and in purulent pneumococcal meningitis.

As at present both in America, (Lederle, New York) and in Denmark (State Serum Institute, Copenhagen) rabbit sera are available against the higher types of Cooper, one is obliged to determine these higher types, too, in the cerebrospinal fluid by the Neufeld method. We found this to be quite well possible with the aid of diagnostic mixed sera. Thus we found without difficulties in a short time once type 23 and once type 14. For this the cerebrospinal fluid must contain a sufficient number of pneumococci. At Groningen we dispose of stock sera against all types, which is the more important as in this country some cases have become known of meningitis finally cured by a combined treatment with sulfapyridine and serum (6).

As a direct result of the figures obtained one can say that typing

is of great theoretical importance. Any theoretical consideration of the pathogenesis of the various pneumococcal affections of the lung must necessarily take into account the differences in type distribution between the individual morbid conditions.

Summary.

1. From March, 1935 to September, 1940 in Holland 560 pneumococcus strains were typed from various pneumococcal infections in adults (over 12 years).

2. The Neufeld method and direct inoculation of a thoroughly washed sputum flake in serum broth are recommended for rapid typing.

3. Sent-in sputa must be inoculated into mice when the type is not found by immediate typing.

4. Capsular swelling must be demonstrated for determining the type. Slide agglutination is not always specific.

5. In lobar pneumonia and empyema type I takes the first place with 58.5 pcl as a causal organism. Then follow the types II (12 pcl), 7 (9.5 pcl), III (9 pcl), 5 (6.5 pcl) and 4 (2.5 pcl). The higher types of Cooper are practically of no significance in lobar pneumonia. In meningitis the types I and III prevail, but higher types are relatively frequent. In bronchopneumonia and bronchitis type I is absent; type II, III and 6 are rather frequent here, and so are the higher types of Cooper.

6. 3 pcl of the 560 strains could not be typed with Lederle diagnostic sera. The types 25, 27 and 32 did not occur among the 560 strains.

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Benzol and the blood picture.

A collocation of the literature and a case of chronic benzol
poisoning.

By

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In 1898 Santesson's paper »Cases of chronic poisoning with coal tar benzene» was published. Since then many investigations and descriptions of chronic benzol poisoning have seen the light of day. Hamilton says that Santesson has become a classic within the literature on benzol poisoning. Hamilton's excellent monograph has itself become a classic. Unfortunately it only comprises literature up to 1930. The following paper attempts to collocate later literature also.

Chemistry and poisonousness.

Benzol is the mother substance of the majority of aromatic compounds and plays an enormous part in the chemical industry, above all in the manufacture of dyes and explosives. Benzol consists of a liquid hydrocarbon, which is formed when organic substances are heated, and is present in coal tar and coal gas. Crude benzol also contains toluol and smaller quantities of xylol, cumol and cymol. Pure benzol is a mobile fluid, clear as water, with a strong etheric smell, congeals at 0° and boils at c. 80°. Benzol is difficult to dissolve in water, 1000 parts of water dissolve 0.8 parts of benzol at 22°. Its solubility in serum is somewhat greater. Benzol is a good solvent of volatile and fatty oils, camphor, rubber, alkaloids, phosphorus, sulphur, bromine and iodine. In commercial benzol there is always thiophen, the boiling point of which is about 84°.

Cases of acute poisoning are most frequently due to accident. The symptoms manifest themselves in headache, vertigo, difficulty in breathing, and by degrees a state of excitation, and finally unconsciousness and death owing to paralysis of the respiration centre. Pathological anatomical findings are very sparse. Kobert expresses this in the words «a poison which can kill without causing severe anatomical changes». In the internal organs small hemorrhages can be observed. Several authors consider it characteristic that the blood is able to remain fluid for a long time, with no signs of hemolysis. Individual susceptibility is very varied. A short contact with benzol may result in death, while in other cases a person who is exposed to the poisonous effect for a longer time escapes. The point of attack for benzol is said to be the central nervous system, the peripheral vasomotor and the myocardium (Charlier 1939). Pure benzol is stated to be about 6 times less poisonous than the crude commercial commodity. The toxic effect is said not to be due to the thiophen content, but to products belonging to a fraction with a boiling point about 80.4—81.2°.

In experiments on animals a concentration of 20 mg of benzol per litre of air proved to cause restriction of movement in the animal, while a conc. of 40 mg per litre of air rendered the animal quite unconscious. In experiments with guinea-pigs, Peronnet (1935) found that 20 mg of benzol per litre of air induced sleep within 5 min. The blood concentration was then 2.6 mg %. With a lower benzol content, sleep was not induced until after a longer period. The blood conc. had then attained the same value.

In experiments with dogs and cats which had to inhale a benzol atmosphere of 9 mg of benzol per litre of air, Lehman could find no changes in dogs even after 4 weeks' experiments. As a rule the cats developed lung affections after 3—4 days and died.

In investigations in different industries an atmosphere containing 100—125 parts of benzol per million proved to have no effect on the blood picture or inorganic sulphates (Davis 1940). Earlier investigations showed that a conc. of 10 per 10,000 involved a risk of fatal poisoning.

The metabolism of benzol.

Outside the organism benzol can be oxidized to carbon dioxide, oxalic acid and fatty acids. Some of the benzol which is taken up by

the organism is removed by way of the respiratory channels. Within the organism the benzol molecule must either be slit up or oxidized and then combined with sulphuric acid or glycuronic acid. As a rule substitution derivatives are attacked more easily than benzol. The metabolism of benzol within the organism has been an obscure matter. Naunyn-Schultzen (1867) proved that some of the benzol changes to phenol. Jaffé (1909) showed another way of breaking down benzol in that the organism split the benzol ring into muconic acid, which was later excreted with the urine. The quantity of muconic acid excreted amounted, however, only to 0.3 % of the original quantity of benzol. According to Jaffé, considerable quantities of benzol are broken down into muconic acid, but this latter is then rapidly oxidized. According to Thierfelder and Klenk (1924), if the benzol was introduced intraperitoneally a quicker resorption was obtained and a larger amount of muconic acid; about 3.7 % of the original amount of benzol, was excreted. The organism then has not time to break down the more rapidly formed muconic acid. Fuchs and Soos (1916) were able to establish the presence of muconic acid in patients who received benzol.

Mori (1918) and Neumacher (1922) were not able, however, to confirm the rapid oxidation of the muconic acid, about 73 % of muconic acid, which was administered subcutaneously, being excreted. Drummond and Finaz (1938) have further studied the behaviour of muconic acid within the organism. Muconic acid met with in urine consists of the trans-trans form. The cis-cis form which appears when benzol is oxidized would have been expected. If the different acids are administered subcutaneously about 50 % of them is excreted in the urine. No change from the one to the other could be established. In animals treated with benzol a change from the cis-cis form to the trans-trans form could take place.

The destruction of the benzol ring within the organism is still obscure.

Gadaskin (1928) was able to prove the presence of benzol in the blood after administration by infiltration, subcutaneously and per os. It was proved most rapidly after the first-mentioned method of administration. The benzol was partly converted into phenol, and the poisoning picture was said to have been due partly to benzol and partly to phenol. After the administration of benzol, Tschernikow and his co-workers (1931) were able to establish the presence

of phenol in the blood. The liver of cats, rabbits and fish oxidized benzol to phenol in irrigation experiments. In frogs phenol could be found even after liver extirpation, so that it is probable that other tissues are also able to oxidize benzol. According to Gueffroy and Luce (1937), with the inhalation of benzol a transient retention arises in the excretion of ether sulphuric acids in the urine, which are later excreted to an increased extent. Schrenk, Yant and Sayers (1936) and Kammer, Isenberg and Berg (1938) attach great importance to this increase in ether sulphuric acids, and are of the opinion that a decrease in the inorganic fraction of sulphur in the urine of 20—30 % is pathognomonic of benzol poisoning.

As an example of the effect of benzol on other tissues may be mentioned the investigation of Underhill and Harris (1923), which showed that benzol influences the metabolism of the muscles, which is reflected in a great increase in the excretion of creatine and the excretion of total-N immediately after the subcutaneous administration of benzol. According to Hess (1935) the splitting up of carbohydrate in the liver is also increased.

Palladin and Ferdmann had already shown that phenol is detoxicated better on an acid diet. Braunstein, Parschin and Chalisowa (1931) and Hunter (1939) point out the influence of diet on benzol metabolism. Acid diets have a more neutralizing effect.

Several papers have been devoted to the influence of vitamin C on benzol intoxication. As a rule lowered values of ascorbic acid excretion in the urine are given. The ascorbic acid values in the blood are also said to be reduced. Friemann (1936) considered the low ascorbic acid values to be a »früh» symptom in benzol poisoning. According to Hagen (1938) and Meyer (1937), ascorbic acid could prevent injury and even repair injuries which had already been caused in experiments on animals. In Friemann's experiments on animals the fall in leukocytes was absent in the animals which had been treated with ascorbic acid, at the same time as the blood-forming organs remained intact. Bormann (1937) was only able to establish that the animals treated with ascorbic acid lived longer than those not so treated. The chronic poisoning picture could not be prevented, however, only postponed somewhat.

According to Danielopolu, Marcon and Gingold (1936), luminal has a checking effect on benzol intoxication.

Trade groups.

Benzol is the mother substance of the majority of aromatic compounds and therefore plays a very important role in the chemical industry, above all in the explosives, dyes and drugs industries. Benzol is also used as an extraction medium and a solvent in a number of industries, among which may be mentioned lac and rubber factories, shoe factories, the linoleum and imitation leather industries. In the manufacture of preserved goods cement substance containing benzol is sometimes used. In the printing branch benzol is used for intaglio-printing and brominechromolithography, and further it is used at chemical cleaning establishments, and for the manufacture of certain polishing and cleaning materials.

As a rule benzol is conveyed to the organism by way of the lungs, the work being performed in an atmosphere containing benzol. Poisoning can also take place if the benzol comes into contact with the skin, as up to 80 % of the benzol, which is fat-soluble, penetrates even unbroken skin. In more infrequent cases benzol has been conveyed by way of the digestive organs. The swallowing of small quantities by a person who was in the habit of sucking up benzol in a siphon and spitting out the remainder, gave rise to a case of chronic poisoning, according to Direkhoff (1932). In rare cases it has been used as an intoxicant.

The great majority of cases of poisoning come from rubber industries of various kinds. Among rubber workers (32 men and 10 women) Arnoldson and Hausser (1938) found a moderate anemia in 73 %, and more pronounced anemia in 35 %. Leukopenia was present in 81 %. At a rubber factory Dimmel (1934) found 66 cases of chronic poisoning, 5 of which had fatal issues. He also describes mass poisoning among the women working at a condom factory. At a place where a solution of rubber in benzol was used for rubber boats, Holstein (1937) found in a third of the workers typical troubles resembling those in chronic benzol poisoning. In 11 cases there was leukopenia with thrombopenia. In a similar occupation, Pabst (1937) found onsetting symptoms in 17 % of the workwomen, in 3 cases severe anemia with thrombopenia. Laignel-Lavastine, Levy and Desoille (1928) report a case with fatal issue in a woman occupied in sticking together impermeable products. Rohner, Baldridge and Hansmann (1926) mention a man who cut up pieces of rubber in a vessel of benzol and succumbed in a hemorrhagic diathesis. Vercelloti (1928) describes one case and Szekely (1935) five cases ending fatally in the rubber industry. Two cases

are given by Schneider (1931), one of which was fatal. During a 4-year period v. Jagic and Khaum (1938) examined 600 persons who were exposed to benzol in rubber factories and lac-printing work, and found 66 cases with early symptoms. In 21 (15 women) a progressive hypochrome anemia was established and in 41 (33 men) cases a granulocytopenia. In an examination of 139 workers in the lac-colour spraying industry Adler-Herzmark and Selinger (1931) found changes in the form of leukocyte decreases with granulocytopenia. Cobet (1938) describes a case of chronic benzol poisoning as a result of enamelling work. According to Lande and Kalinowsky (1928), benzol-lac gives rise to a picture resembling leukemia, and according to Lederer (1932) to a form of illness resembling Morbus Gaucher. Among 39 workers in intaglio-printing Adler-Herzmark and Selinger often found depression of the erythrocytes, and in a mass poisoning among workers in intaglio-printing, Ehrhardt (1936) found 12 persons with leukopenia, in the majority of cases lymphocytosis and thrombopenia, but no hemorrhages. Andersen (1934) describes a case of benzol poisoning in workers in bromine chromolithography. In an examination of printers, Brocher (1929) found two cases of pronounced benzol poisoning. Gray, Greenfield and Lederer (1940) report a case in a colour-printing worker. In Arnoldson and Hausser's statistics of 280 men employed in the intaglioprinting industry anemia was found in 65 %, among whom it was more pronounced in 35 %, and leukopenia in 74 %. Glibert (1936) gives an account of about 50 cases, one of them with neurological symptoms, which had originated from mirror enamelling. Torday (1935) and Stodtmeister (1938) each report one case of benzol poisoning in printers. Brocher (1929) adduces slightly increased erythrocyte and leukocyte values in a large number of printers as a preliminary stage to the aplastic phase. From an alkaloid factory where benzol is used as an extractive Mitznik and Genkin (1931) describe 7 cases of chronic poisoning. Gall (1938) mentions a leather-worker who used benzol preparations for 4 years and succumbed from gastric hemorrhage. From a shoe factory Lamy, Kissel and Pierquin (1938) report 11 cases who became ill when a new adhesive containing benzol was first used, 4 of them dying.

In an examination of 60 men and 16 women employed in factories whose products contained benzol, Nikulina and Titowa (1934)

found a thrombopenia in 58 men and 15 women. Leukopenia was present in 50 % of the cases, anemia only in a few cases. Montegrosso (1938) reports 4 cases of chronic benzol poisoning, and Hunter (1939) reports 89 cases of chronic exposure to benzol.

Symptomatology.

The commencing symptoms are not pronounced and are capable of various interpretations. The patients usually complain of headache, fatigue, vertigo, poor appetite and sleeplessness. Some of these symptoms can be explained by simultaneous anemia. By degrees a pallor appears which is noticeable even to the associates of the person in question. Cutaneous hemorrhages appear from the most insignificant trauma. Hemorrhages begin to appear from the mucous membranes, often as troublesome bleedings from the gums, repeated nose bleedings, increased and more frequent menstruation. In advanced cases also hemorrhages from the digestive canal, and in rare cases also from the retina.

In the cavity of the mouth necrotic ulcerations are often observed and are due to secondary infection, owing to the decreased leukocyte defence of the tissues. Fever is often observed and is partly due to secondary infection, but in many cases without infection. The fever curve can sometimes assume an undulating course and may probably be considered a bone marrow reaction. Ask-Upmark (1938).

From the circulation organs palpitation of the heart and breathlessness are chiefly noticeable in the first place and are partly due to the anemia. Mignolet (1939) gives prominence in particular to hypotonia as characteristic of benzol intoxication, which, according to Dautrebande, paralyses the vasomotor. Animals treated with benzol cannot react with blood pressure increase after the administration of adrenalin, as do animals which have not been treated. From the respiratory organs, dryness in the pharynx and throat are often indicated. Gigon mentions frequently pronounced redness of the mucous membrane of the mouth. Mitznik and Genkin (1931) found several cases of bronchial asthma among benzol workers.

Among digestive symptoms, loss of appetite is most frequently indicated. Vomiting sometimes occurs. Mignolet considers that he found strikingly many cases of dental caries among benzol workers.

Examinations of the gastric juices usually showed that hypochylia was present. Weil-Aschkenasy (1938) usually found hypochylia, and in some cases histamine refractory achylia. Disturbances of the liver are stated to be usual, particularly among rubber workers, according to Arnoldson and Hausser (1938).

The endocrine organs may also be affected. In an examination of Viennese workmen, Adler-Herzmark and Selinger (1931) observed a striking number of cases of Basedow's disease. Itching of the skin is often indicated, and eczema sometimes occurs.

In the majority of cases chronic benzol poisoning leads to injury of the blood-forming organs, affording a symptom picture resembling that of aplastic anemia. In certain cases a stimulation of bone marrow, an increase in certain elements, and even a change to leukemia can also be observed. Penati and Vigliano (1938) indicate four possibilities of blood changes, 1) aplastic anemia, 2) hypoplastic anemia, 3) atypical aplastic anemia with hyperplasia in the liver and spleen, 4) genuine leukemia. The blood symptoms group themselves mainly round the triad anemia, purpura and granulocytopenia.

As a rule anemia is a late symptom. No relation appears to exist between erythropenia and leukopenia. Generally the anemia is moderate. Hamilton (1931) reports only 15 cases out of 70 with anemia below 1 million red blood corpuscles. The majority of authors mention poikilocytosis and anisocytosis. Hunter (1939) and Hanflig (1927) observed strikingly different sizes and in particular small forms. On the other hand Gall (1938) found unusually many macrocytes. According to Whitby and Britton (1937), the changes in the size of the blood corpuscles are only inconsiderable. Sometimes an erythroblast or two can be observed. As a rule there is no polychromasia, and the reticulocytes are very scanty, a sign of the reduced erythropoiesis.

The hemoglobin falls almost parallel with the erythrocyte values. The colour index is usually about 1 or somewhat above that, according to Hamilton. Later authors, such as Arnoldson and Hausser (1938) and Weil and Aschkenasy (1938), usually found indexes above 1. In Mignolet's series also the index was raised. If the anemia is increased, the index also rises as a rule. (Smith 1928).

One of the most characteristic features is the pronounced leu-

kopenia. The values are usually between 1000—2000 per mm, but in severe cases may approach nil. It is above all the granulated cells which are reduced and sometimes disappear entirely. If any infection with suppuration should appear, they may be increased temporarily. According to Gall, myeloblasts and myelocytes are sometimes met with, and this has also been observed by Hunter and Hanflig and by Matthes (1937).

Opinions are divided as regards the eosinophil blood corpuscles. Meyer (1931) considers eosinophilia characteristic of chronic benzol poisoning. Weil and Aschkenasy and Glibert (1936) and Hunter (1939) considered that eosinophilia was often present and indicate early marrow injury. The figures for eosinophilia, which are often given are, however, of but little significance for genuine eosinophilia. Nor does Mignolet consider that there is any increase, if the absolute figures are taken. The significance of the eosinophil blood corpuscles is a matter of dispute. According to some it is a bad sign, according to others a sign of recovery. Weil and Aschkenasy consider the occurrence of eosinophilia more pronounced in men. Thanks to their chemical constitution, the eosinophil blood corpuscles have greater powers of resistance than the other leukocytes.

Meyer (1931) often established increases in the basophil elements and the appearance of plasma cells. Paul, Friedländer and McCord (1929) state that an increase in the basophil blood corpuscles is an early symptom. The number of thrombocytes is decreased as a rule, which is one of the classic symptoms. Mignolet considers that it is one of the earliest symptoms. Nikulina and Titowa (1934) are of the same opinion. Kern (1938) describes a case of isolated thrombopenia in chronic benzol poisoning, where the blood picture was only slightly depressed for the rest. It is particularly in the final phases that the low values are met with; sometimes they may disappear entirely.

The coagulation-time is stated to be protracted as a rule. According to Mignolet, the prolongation is an early symptom and may possibly remain long after the majority of other symptoms have receded. The osmotic resistance is normal.

Among other results of blood-urine examinations, the calcium values in the blood are stated to be reduced, and a decrease in the inorganic fraction of the sulphur in the urine is indicated. A de-

crease to 70—80 % in the inorganic fraction of the total sulphur is said to be significative of chronic benzol poisoning.

It is in the first place the acute poisonings which present severe neurological symptoms, in the form of headaches, delirium, clouding of the mind, and finally unconsciousness. The chronic poisonings also present neurological symptoms. The patients complain of sleeplessness, trembling, twitchings of the muscles, a general feeling of depression, sometimes of sleepiness, and are often stated in the case-books to be asthenic. Strikingly often they are intoxicated with minimal quantities of alcohol, as e. g. after a glass of ale.

Among the more unusual observations, Korvin (1933) describes a case of epilepsy in connection with chronic benzol poisoning. Korvin cites a case described by Goldman of a retrobullar neuritis. Glibert (1936) adduces a polyneuritis picture, and Lande and Kalinowski (1928) a case of medianus neuritis in a patient who had used benzol on his arms and hands. Kern (1938) also quotes a neuritis in n. ischiadicus and paralysis of the extremities, probably arising as a result of purpura cerebri. Bumke mentions the occurrence of funicular myelitis. Glibert and Albrecht (1932) each report a case of papillary stasis. In the former case even a relieving trepanation was performed.

The explanations have in general been considered to be purpura hemorrhages in different places in the nervous system. According to Korvin, benzol directly injures nerve elements.

Among more unusual symptoms may be mentioned a picture resembling Morbus Gaucher, described by Lederer (1932). Mallory-Gall-Brickley (1939) point out that although splenomegali was rarely apparent clinically, the spleen was often enlarged at autopsy.

Course.

The majority of authors consider women and younger persons more susceptible to the influence of benzol than men. More recent authors also hold similar opinions. Adler-Herzmark and Selinger (1931) consider anemia more usual among women, while men recover better. Osgood (1932) and v. Jagic and Khaum (1939) are of a similar opinion — that anemia affects women more often, while leukopenia more often affects men. Dimmel (1933) and Hunter (1939) do not consider women more susceptible than men. Mallory-

Gall-Brickley (1939) consider hyperplastic reactions occurring more commonly in males, hypoplasia in females. Pregnancy has been thought to increase the susceptibility of the organism to benzol intoxication, and also chronic infections. The fact that women are more often attacked Engelhardt (1931) considers to be connected with their more frequent employment within these occupations.

There is a great individual variation in the susceptibility to benzol. The individual degrees of susceptibility, the duration and the degrees of concentration will of course determine the intoxication. Some consider that if susceptibility is present, it should show itself with the first few years, and that a long exposure should lead to a certain power of resistance. Hunter thinks that it is impossible to become inured. In Schneider's case deterioration of the blood did not take place until after 35 years' work within the same industry. Different figures are given with regard to the time benzol requires to give rise to intoxication. The minimum time is naturally of the greatest interest. Santesson mentions periods from one week to several years. One of the cases who had only worked with benzol for some weeks succumbed, while those who had been exposed for several years escaped, which again emphasizes the great variations.

Benzol poisoning is extremely insidious. Even if persons have been removed from its noxious influence and received treatment, relapses may be met with. Brocher (1929) cites a case which recovered at first, but after 2 months fell ill again with hemorrhagic diathesis and succumbed. It is very often stated that the symptoms began after the patient had left the dangerous occupation. Santesson observed how in 4 cases the hemorrhagic diathesis did not appear until after they had ceased to work in the factory. In Selling's first case — a woman — the symptoms did not appear until after she had given up her work. In one case Cobel (1938) mentions explicitly continued deterioration, in spite of the work having been given up. Rohner, Baldridge and Hansmann (1926) mention a case where hemorrhages appeared 2 weeks after the cessation of work. Dimmel (1934) also cites a case where the symptoms appeared 3 weeks after the cessation of work, in spite of which death took place within a week. Stodtmeister describes a case which recovered, but had a severe relapse after 2 years. Berg (cit. Schulten) mentions a patient who was employed from the age of 18 to 28 in benzol

work but then gave up that occupation. At the age of 38 the patient was attacked by severe anemia with hemorrhagic diathesis. Thus in respect of the possibility of exposure to benzol, it was necessary for the anamnesis to go sufficiently far back. When using benzol as a therapeutic in leukemia, Koranyi (1912) also observed how the white blood corpuscles continued to decrease in number, although the benzol was stopped.

As a rule the course is chronic, and recovery takes place slowly and is sometimes interrupted by temporary setbacks. In cases with a fatal issue the duration after the onset of symptoms usually varies from 1—3 weeks. In Santesson's collocation the shortest period was 10 days. Martland describes an acute case with a duration of only 5 days, and Dimmel cites a case where death took place 10 hours after the acute symptoms had appeared. Rises in temperature are often met with, particularly in association with relapses. Infections need not be present, and blood cultures are negative as a rule. By way of explanation, the absorption be of breaking-down products has been given, but it might also be due to bone-marrow reactions. (Ask-Upmark). If the case recovers, the blood picture does not become normal until after the lapse of months, and sometimes a thrombopenia or changed coagulation time remains as a residuum.

Path. anatomy.

Thanks to its lipid solubility, benzol is concentrated principally in the bone-marrow and brain. Schneider (1931) considers that there is a connection between lipid metabolism and sensitivity to benzol. Women, with their more developed subcutaneous layer of fat, are more sensitive to benzol than men. Schneider also calls attention to a case where the benzol intoxication seemed to appear in association with a great increase in weight.

The typical blood changes accompanying benzol intoxication are due to changes of a degenerative nature in the bone-marrow. With aplastic conditions in the bonemarrow there is most frequently an aplasia of all the bone-marrow elements. Various substances, however, have different affinities with different bone-marrow elements, and it is possible to meet with injuries which only affect certain forms of cells. In the case of benzol injuries, leukoblast and thromboblast tissue is as a rule attacked in the first place, and erythroblast tissue last. Baserga is almost the only one to

have stated that erythroblasts are injured in the first place. Clinical experience also argues in favour of the first-mentioned tissues being affected by benzol in the first place; the relative order may vary, however. Isolated thrombocytopenias are described, and many authors give thrombopenia as the earliest symptom. Schulten (1939) considers that in benzol poisoning the megakaryocytes disappear from the bone-marrow first, while the erythroblast tissue is the last to be attacked. Aplastic phenomena from the bone marrow may be due either to the most primitive cells having been damaged, or to the injury having affected a later stage of development, giving rise to a check in maturity. Tzank considers that he has found a great check in development in the bone-marrow with chronic benzol poisoning.

The first exact autopsy findings are given by Santesson, who found hemorrhages in the skin, pericardium and myocardium, and from the alimentary canal. The bone-marrow is stated to be of normal consistency with dense hemorrhages. In Hamillon's extensive collocation the most usual finding was an aplastic marrow; in 2 cases only was a hyperplastic condition present. As a rule the occurrence of aplastic marrow is mentioned, but, particularly in recent years, there have been several observations of hyperplastic bone-marrow reactions, most frequently of the myeloid elements. Gall describes a case with extra medullary metaplasias in the spleen and liver. Andersen (1934) reports a case of hyperplastic marrow in an inkling-printing worker. Mallory-Gall-Briekley (1939) describe histologic material from 19 patients with histories of chronic benzol exposures and only 6 showed hypoplasia, none aplasia, three had normal marrow, three increased and 5 marked marrowhyperplasia. In a number of cases a transition to genuine leukemia had occurred. Benzol is not only a poison for the bone-marrow, the circulating leukocytes are also injured. Ronchelli, quoted by Hamillon, calls attention to the rapid recovery in a case of lymphogranulomatosis which was treated with benzol, after the benzol was discontinued. The recovery was too rapid to have been due only to the regeneration of the bone-marrow. Miller (1931) holds a similar view on the injury caused by benzol to the circulating leukocytes and thrombocytes. Mignolet points out how, in different conditions of irritation, a pouring-out of leukocytes, for the most part immature forms, a

so-called leukocyte rain, may be obtained in aplastic conditions and partly hyperplastic marrow areas. In cases of benzol poisoning the appearance of immature forms of leukocytes is sometimes met with, which is said to originate from such bone-marrow areas.

During recent years a large number of sternal punctures have been effected in cases of benzol poisoning. As a rule an aplastic marrow has been found, but in not a few cases hyperplastic reactions have been met with. Matthes found an aplastic marrow in 2 cases. In a classic case Budelmann (1938) found «a marrow not all too poor in cells». In a case which improved, but later disimproved spontaneously, Stodtmeister (1938) observed a marrow with abundant cells but numerous immature forms. Weil and Aschkenasy, who made several sternal punctures, found a tendency to aplasia already in the latent cases, in men most frequently a partial tendency to aplasia with a tendency towards lymphoid reaction. Myeloid reaction was observed only once and erythroblast reaction twice, the latter in women. Lamy, Kissel and Pierquin (1938) found aplastic marrow in the severe cases, in the milder cases only a decrease in the granulating elements and, if anything, an erythroblastic reaction. Perrin, Kissel and Pierquin (1938) speak of an acute case in which the sternal puncture showed an increase of the myeloid elements. In his monograph on sternal punctures Rohr (1940) states that in benzol injuries aplastic marrow is most frequently found, but in a number of cases hyperplasias with increases in myeloblasts and erythroblasts. The myelogram is very valuable when it is necessary to make a diagnosis, but still more important for making the prognosis. Rohr says, however, that the atrophies may be scattered in foci and perhaps not appear in the punctate, and that hyperplasia and atrophy may vary in different places.

The importance of the constitution factor has been repeatedly emphasized, at the same time as attention has been drawn to the importance of previous affections of the reticulo-endothelial apparatus, which have created a more favourable point of attack for later injurious agencies.

In parenchymatous organs the occurrence of fat metabolism and degeneration is often mentioned. Hemosiderosis is not usual, but is described in a number of cases. In his case Direkhoff (1932) established great deposits of pigment in the liver and spleen. He-

mosiderosis might be explained as due to hemorrhage in the tissues. The resorption of hemorrhages would lead to the deposition of iron in the ret. endothelia apparatus. The destruction of blood corpuscles which had been transfused may also give rise to siderosis. According to Gall, it would be explained by the depressed marrow not having been able to utilise the iron released by the destructed blood corpuscles to produce sufficient blood corpuscles. It is possible that the bone-marrow could only produce erythrocytes which were not quite perfect but were more rapidly destroyed. No change in quantitative fragility test has been met with, however.

Experiments on animals.

The first experiments on animals were made by Santesson, who administered benzol and benzine to the animals, partly subcutaneously by injection, and partly by means of compresses, and finally by inhalation. In the last-mentioned case no effect was observed. The blood values are not stated, but on the other hand he found hemorrhages in the pleura, lungs and mucous membranes. Many experiments have been made on animals since that time. In general the method indicated by Selling has been employed, and mixtures of equal parts of benzol and olive oil injected. The doses have been relatively large: 0.5—1—2 cm³ daily for some weeks. Wallbach (1932) has tried to titrate out the smallest dose which is necessary to obtain depression in the white blood picture. The minimum dose appears to be about 0.1—0.2 cm³. Smaller doses did not decrease the number of leukocytes. Beyer (1933) was unable to evoke any changes with 0.01 cm³.

As a rule rabbits have been used as experimental animals. According to Wallbach (1932), benzol was only able to give rise to leukopenia in rabbits and dogs, but on the other hand not in guinea-pigs, mice or fowls. Attention is constantly called to the great individual variation. Pappenheim stated that benzol does not appear to affect certain breeds of rabbits. Neuman (1915) and Schillowa (1933) also emphasize the great difference in the mode of reaction, in that some develop leukopenia, others no changes, others again leukocytosis.

What is characteristic of the blood changes is the appearance of a leukopenia, which with Selling's method appears already after a few days, and after six days a decline in the leukocytes of 70 %

can be expected. Even after a single dose a leukopenia may be induced, which does not persist, however, unless the injections are continued. If the injections are interrupted, a slight increase in the leukocytes is obtained, which is followed later by a fresh depression. Much has been written about this diphasic leukocyte curve, which has been described particularly by Weisskotten (1916). The second depression has been set in connection with the antibody-antigen reaction, the increase in association with regeneration in the bone-marrow.

After the administration of benzol, Woronow (1929) at first found falling leukocyte values, which rose immediately before death. The leukopenia induced by a small number of injections often persists a long time, which is a sign of serious injury to the bone-marrow — in Weisskotten's case for about a year.

The change in the red blood corpuscle picture is not so striking. The decrease in erythrocytes does not appear until after a considerable period of administration. Statements are somewhat divergent. Langlois and Desbouis (1907) found a strong polycythemia in rabbits, guinea-pigs and pigeons after they had inhaled benzol, but their experiments could not be reproduced. Orzechowski (1929) found no change in the red blood corpuscle picture. In contrast to this, Baserga (1932) considered that the erythropoietic system was injured earlier than the myeloid system. Miyamoto (1937) found at first a decrease in all the blood corpuscle elements, but later an increase in leukocytes. As a sign of the depression of the red blood corpuscles, Uno (1933) established reduced reticulocyte values in rabbits after benzol injections. Feller (1937) observed abundant eosinophils in rats treated with benzol.

Statements are also divergent with regard to the thrombocytes. Orzechowski found no change in the number of the thrombocytes in benzol poisoning. On the other hand Weisskotten found an increase at first. Similar findings were also made by Beyer (1933) and Minot-Bruckman. In contrast to this Müller (1931), states that in rabbits benzol gives rise to a thrombopenia, which he says is due to injury to the megakaryocytes. Medlar (1935) observed the appearance of megakaryocytes in the circulating blood after benzol injections. Baserga had noticed the occurrence of giant nuclear cells in rabbits and was of the opinion that this was a sign of great leukocyte regeneration.

The bleeding-time is stated to be normal as a rule. According to Kuntzen (1931), animals which inhaled the gases from a benzol driven motor were more subject to thrombosis. The effect of carbon monoxide must also be taken into account here. The investigation was a link in Payr's contention that there is an increased possibility of thrombosis in large cities.

In Santesson's experiments on animals hemorrhages in the pleura, gastric mucous membrane and pericardium were established at autopsy. In the great majority of cases an affection of the bone-marrow in the form of an aplasia is found. In a number of cases a stimulating influence can also be seen, particularly before the destructive tendencies have gained the upper hand. Schillowa (1933) points out the great individual variations, in that some animals develop bone-marrow aplasia, others react sometimes with hyperplasia, especially at the beginning of the intoxication. With small doses Lignac (1932) was able to induce changes resembling blastomas in mice and indicated the resemblance to leukemia. In experiments on rats Feller was able to establish a lively myeloidic reaction in the bone-marrow.

The leukopenia was said to be due to aplasia of the myelogenic elements. The effect of benzol injections sets in very rapidly, however, and therefore Selling considered the leukopenia to be due to direct destruction of the circulating elements. Ronchetti holds a similar view. Pappenheim, who was of the opinion that the leukopenia is due entirely to the white elements collecting in the capillaries in the spleen, liver and lungs, is almost alone in this opinion. According to Hamilton a similar observation was made by Le Noir and Claude.

Several Russian authors, Nicolajew and Schparo (1929) and also Schestrow and Salistowskaja (1926) consider that benzol dissolves the lipid membrane of the red blood corpuscles which are thereby phagocytized. Benzol would thus be a hemolytic. The leukocyte values are decreased by their stem cells having to take over the erythropoietic function owing to the erythrolysis. Siderosis had also been observed. In general, however, the opinion is held that no hemolysis occurs. Siderosis can be explained by bleeding in the tissues.

Weisskotten and Sacki (1938) found no difference in the benzol effect on splenectomized and normal animals. Paschkis and Kulka (1927) found that if rabbits were »supravital stained» benzol poisoning led less readily to aleukia.

The bone-marrow is not the only organ to be attacked. Levi describes changes in the thymus in rabbits treated with benzol. Hett (1938) and Hett and Maak (1938) found atrophies of the generative organs in mice after inhalation and subcutaneous injection of benzol.

In animals which had inhaled benzol Schmidtman (1930) established emphysemas, chronic bronchitis, epithelial hyperplasias and metaplasias, but without destructive tendencies.

In general the benzol-intoxicated animals exhibited decreased powers of resistance to infections in comparison with normal animals. This reduced power of resistance is said to be due, firstly, to the decrease in the number of leukocytes, and secondly, to the decrease in the formation of antibodies as a decreased lysin-precipitin-agglutinin titre. In general a reduced formation of antibodies is found with the administration of substances which have a destructive effect on bone-marrow, while substances which irritate it give rise to an increased production of antibodies.

Benzol has been very much used in studies of infection conditions in cases of leukopenia and also of the reaction of the leukopenic organism to different chemical and physical irritants. The benzol animals readily caught infections. As a rule they could not respond with cellular reaction, but the bacteria were free to commit their ravages [Müller (1931)]. If the leukopenia was less than 2,000 white blood corpuscles, the animals could not hold their own against the invading bacteria. If the animals had more than 2,000, their blood picture reacted like that of a normal animal. Even a latent infection could be made to flare up anew by means of benzol. Wallbach established the fact that, if the experimental animals had a spontaneous infection, they most frequently became extremely resistant to benzol and could be sprayed for months without developing leukopenia. Streptococci infections had no retarding effect, but on the other hand injections of peptone would retard the leukopenia.

With croton oil and heating up to 55° no leukocyte infiltration was obtained in experiments with leukopenic animals in which the white blood corpuscles had fallen to 1,000, as in the case of normal ones. Experiments with anaphylactic shocks on benzol-poisoned guinea-pigs showed a reduction in the leukocytes of 30—50 %, as in normal ones [Bonnanno (1931)]. Nor could Testolin (1932)

find any change in the reaction in cases of hemoclastic crises. Steiner (1932) found the remarkable fact that with repeated benzol injections on guinea-pigs, the animals died after 3—4 injections with a picture resembling anaphylaxis. It differed from ordinary anaphylaxis, however, in that it was not possible to transfer it, and that the animals did not react to adrenalin. Rats, which are difficult to cause to react anaphylactically, also reacted in the same way. The pre-condition was, however, that the later injections should be given in the area inflamed by the preceding injection. The resorption was much more rapid and corresponded fully to the reaction obtained if the injection was given intravenously.

The stimulating influence of benzol.

At an early period it was found that in certain cases small quantities of benzol had a stimulating effect on erythropoieses. Among the earliest observers are mentioned Langlois and Desbouis (1907), who obtained picture resembling polycythemia in guinea-pigs after benzol injections. It has not been possible to repeat their experiments, however. In some experiments Selling also reported a slight increase of the white blood corpuscles. The same condition has been observed by several authors. Schillowa (1933) often found leukocytosis and an increase in thrombocytes at the beginning of experiments on animals. Similar findings were made by Müller (1931). Baserga (1931) mentions the occurrence of large polynuclear cells in the blood, indicating great irritation of the myelogenic system. Beyer (1933) who employed very small doses of benzol, found an increase in the thrombocytes but little effect on the other blood corpuscle elements. In inhalation experiments on rats, Schmidtman (1930) found leukocytosis in the beginning, and similar findings were also made by Engelhardt (1931). With small quantities of benzol, Osgood (1932) was able to obtain an increase in all the blood corpuscle elements, but on the other hand great depression with larger dosis. Miyamoto (1937) at first found a depression of all the elements and later a leukocyte increase. In experiments for the purpose of studying the effect of benzol on tissue cultures Guercio and Arnone (1935) could not find any stimulating influence. According to Wallbach (1932) benzol in small quantities increases the granulocytes and gives rise to youthful forms.

Genuine leukemia forms in animals are described by Lignac (1932), who succeeded in obtaining leukemia pictures in mice with small quantities of benzol.

In man also benzol in small quantities is stated to have a stimulating effect on the bone-marrow and in certain cases to give rise to leukemia. Pappenheim, Hultgren (1926) and Leconte found that small quantities of benzol stimulated the leukopoiesis. Floret, cited by Hamilton, found increased hemoglobin and leukocyte values in women who worked with benzol.

Audaciously enough Hajos (1926) recommends it in cases of secondary anemia and is of the opinion that he has seen good results (!) while in healthy persons benzol leads to a transient hyperglobulia. When benzol was used for therapeutic purposes in leukemia cases, Koranyi and Billing found an increase in red blood corpuscles and leukocytes to begin with.

An actual transition to leukemia is described by several authors. Delore and Borgomano (1927) described a case of chronic benzol poisoning which ended as lymphatic leukemia. Falconer (1933) also gives an account of a case of lymphatic leukemia after benzol, verified at autopsy. In this case it had been possible to follow the blood picture for 4 years. Martland, quoted by Hamilton, observed a gastro-intestinal leukemia in a case of benzol poisoning. Penati and Vigliano (1938) report about 10 cases of myelogenous leukemias after benzol Mallory-Gall-Brickley (1909) report of 2 cases with leukemic pictures. Weil and Aschkenasy (1938) could not find among their cases any signs of irritation in the form of polyglobulia or leukocytosis. Henning and Keilhack (1939) point out the connection between agranulocytosis — aplastic conditions and acute leukemia. Segerdahl (1934) also describes a case of leukopenia with an acute myelogenous leukemic final stage. Henning apprehends the different pictures as different stages in the same bone marrow disease.

Differential diagnosis.

The diseases that have to be differential-diagnosed are above all pernicious anemia, essential thrombocytopenia, agranulocytosis and aleukemic leukemia conditions. As a rule the first-mentioned disease is met with in the higher ages. Glossitis, increased indirect

bilirubin reaction, macrocytosis, achylia, good effect on the liver are clearly characteristic. A sternal puncture may possibly assist the diagnosis. As a rule, essential thrombopenia accompanies increased leukocyte figures, signs of erythrocyte regeneration and enlargement of the spleen. Agranulocytosis exhibits only a decrease in thrombocytes and erythrocytes in the final stages. Chronic aleukemic lymphatic leukemia generally exhibits glandular swellings and also signs of erythrocyte regeneration. In this case sternal puncture may assist on the diagnosis.

Therapy.

In the first place the injurious agent must no longer be allowed to exercise its influence; the person injured by benzol must give up his occupation. Blood transfusions are the only effective form of therapy, and thanks to them it has been possible to save not a few cases. Preparations of liver have not the same effect as in pernicious anemia, even though a certain supporting value cannot be denied them. Hamilton (1931) reports 2 cases where liver was used, apparently with good results. Mignolet (1939) also considered that he saw good effects from liver. Lamy-Pierquin-Kissel (1939) found no very good effects from preparations of liver or ventricle. In some cases raw fetal calves' liver is said to have had an effect where no effect had been seen with ordinary liver.

Opinions are divided as regards the value of splenectomy. Hegler (1938) recommends it and obtained good effects in three severe cases. Schneider (1931) and Budelman (1938) also consider that spleen extirpation may be beneficial. Cain, Cattan and Hertz (1938) tried extirpation in two cases but could not save them. Weisskotten, cited by Gall (1938), could not establish either deterioration or improvement. Morrison and Samwick (1940) recommend the transfusion of healthy bone-marrow intrasternally to patients with aplastic forms of anemia. In the literature there are no reports of its having yet been tried in cases of benzol anemia, but it would be worth testing.

In a number of cases slight doses of roentgen on the hollow bones have been tried, to stimulate the bone-marrow. In certain cases adrenalin injections have been tried. The administration of vitamin C appears to have a supporting effect. Observations on the vitamin C deficit in benzol-poisoned cases and the favourable experiments

on animals formed the starting-point for this form of therapy. Hagen (1938) even considered that, despite the appearance of leukopenia in benzol workers, they could remain at their work if they were given large quantities of vitamin C, which is not advisable, however.

These patients should naturally also be given other vitamins, and in particular the B-complex and iron. On the other hand arsenic is of doubtful value, as it is a bone-marrow depressor. In cases of acute poisoning, Nick (1922) used intravenous injections of 10 % lecithin emulsion, the idea being to bind the circulating benzol in the blood. As a rule preparations of pentanucleotide are considered valueless.

The forms of therapy presuppose, however, that the bone-marrow is not completely aplastic, but that some elements are left, on which the different media can exercise some stimulating effect.

Prophylaxis.

It will of course be an important task to try to decrease the use of products containing benzol by using other less harmful substitute preparations. If this is not possible, the hygienic arrangements should be carefully supervised. Ventilation arrangements should be thoroughly satisfactory; possibly the work should be carried on in places where there is strong air circulation. Vessels containing benzol products should not be left open, but should be closed immediately after use. It should be noted that benzol fumes are heavier than air and sink towards the floor, and therefore the suction arrangements should be placed at a low level. Industries should be carefully informed of the use of benzol in the different phases of the work and in their products.

Information e. g. in the form of notices put up at the places of work might be very useful. In Germany there is a »Benzol-Merkblatt» designed to be hung up at the place of work. On this notice the earliest symptoms and general hygienic directions are given, some of which may be quoted, such as to avoid washing the hands in benzol, to spend the pauses in work out in the open air, a regular mode of life with sufficient rest, a high-grade diet, and care of the teeth.

An entrance examination should be made, and undernourished and anemia persons should not be engaged. Female and juvenile labour should not be employed.

By means of regular examinations of the blood and urine, benzol injuries can of course be discovered early, and the person threatened can be removed from the work. Above all the establishment of thrombocytopenia and leukopenia have been decisive. It is generally thought that a leukopenia below 4,000 white blood corpuscles per mm and especially lowering of the polynuclear percentage and a thrombopenia with 50,000—100,000 are signs of benzol injuries. Similarly a Hgb. value below 80 % and a decrease in the red blood corpuscles of 10—15 % are said to indicate benzol injuries.

In American quarters great importance is attached to a reduction of the inorganic sulphuric acids in the urine, and a decline to only 70—80 % of the total is said to be significative of benzol poisoning. It must be definitely established, however, that no other solvent is used which might give rise to a similar decline.

Complete examinations of the blood should be made every 3—4 months, in the opinion of some as often as every 3—6 weeks. A leukopenia alone must not be allowed to be decisive, but other symptoms also should afford guidance when leukopenia is not present.

Märta P. 16 years. Case record 1145/40.

The parents alive and well. Patient is the 5th of 7 healthy brothers and sisters. No metabolic or blood diseases in the family. No exposure to Tbc. Good home conditions. Food conditions ordinary, does not eat fruit or vegetables to any great extent. Of earlier illnesses, pneumonia as a child. For the rest has always been healthy except for passing colds. Has always been pale. Menarche at the age of 14. Menstruation 3—4 days every 4th week, not particularly abundant.

Since September 1938 has worked at a shoe factory as a stitcher and stuck together pieces of leather with a solution containing rubber dissolved in a mixture of 40 % benzene and 60 % benzol. The pieces of leather are spread out on a sheet of millboard and covered with solution and then sent on to another workwoman. The solution does not come into contact with the hands. The atmosphere is somewhat saturated with benzol. The patient was examined before she began working at the factory and is said to have exhibited no signs of disease then. A blood specimen was not taken. She has been medically examined every year since, the last time in February 1940. The patient states that she was then already appreciably pale, but no blood test was taken.

The patient began to feel tired in December 1939. The fatigue became increasingly troublesome, and during the last few weeks before admission there was breathlessness, especially on movement. No palpitations of the heart of giddiness. No stenocardiac trouble. No hemorrhages from the

mucous membranes of the nose and mouth or from the digestive apparatus. Has noticed no discolorations. The menstrual flow not particularly increased. Has not observed any blood in the urine. No oedema. Appetite poor, but no indisposition or vomiting. Has not lost weight. No loss of hair. Has not observed any brittleness of the nails. Her associates and the patient herself noticed that she grew paler. Admitted to the Med. clinic on 16th April 1940.

Status.

Slender, dark girl. Not affected. Very pale, the visible mucous membranes pale. No cyanosis or dyspnoea during rest. No oedema. Under the mammae and on the abdomen and back and down towards the sacrum the skin is dry and considerably pigmented. No icterus or tendency to a green tinge in the complexion. No cutaneous hemorrhages. Nails and hair without remark. No tremors of tongue or fingers. Tonsils of normal size, teeth healthy. No ulcerations in the pharynx. Thyroidea not enlarged. No lymphatic glands palpable. The heart exhibited no percussible enlargement. No pulsations. Systolic frem. Ictus in I₅ one finger-breadth inside mam. no increase in width or lifting. Systolic murmur over the whole heart, strongest at the apex. Tachycardia but no arrhythmia. Murmur over peripheral vessels. Blood pressure 140/90. Lungs without remark. Abdomen normal configuration, soft, no tenderness, no pathological resistances. Liver and spleen not palpable. Neurological examination without remark, Ophth. without remark.

Hgb. 46 %. Red blood corpuscles 1.9 mill. Index: white blood corpuscles 800. Thrombocytes 23,000. Diff: neutr. 24 %, eos. 0 % lymph. 64 %, mon. 8 %, eos. 4 %, bas. 0 %. Reticulocytes 0 %. Strong aniso- and poikilocytosis. Size of erythrocytes 7.2—7.6 my. Fragility test. max. 0.28 % and min. 0.48 %. Bleeding time 9.5 min. S. R. 69 mm. Further blood examinations appears from the tables.

Other laboratory findings: Nonprotein nitrogen R. N. 30 mg %. Blood culture neg. Wassermann neg. Ecg. Sinus tachycardia and T₂ and T₃ negative, signs of myocardia injury. Test meal: hypochylia, not until after histamine low hydrochloric acid values. Galactose loading: no excretion of sugar, blood sugar values depressed rather. Mantoux neg. Benzol-cutaneous test neg. Sed. without remark. Sternal puncture 16/5 1940: pronounced myeloblast and promyelocyte marrow, only occasional erythroblasts. Sternal p. 12/10 1940: considerable increase of erythroblasts, which now attained normal values. Still a certain displacement to the left in the white picture.

When admitted febrile. Temp. became normal after some weeks but rose again later, subsequently undulating. During the first month no noticeable improvement in the blood values; rather a deterioration during the first weeks. The menstruations were very protracted and very profuse during this period. The treatment consisted first and foremost of repeated blood transfusions. Of other pharmaceutical preparations heptomin, nucleosin, iron, vitamins A, B, C, D. raw liver. After 6 weeks the blood values began to rise slowly, but not until after 6 months had Hgb. reached

about 80 % and the red blood corpuscles 3.5 mill. Persisting leukopenia and thrombocytopenia, and at the most recent examination 9 months later, the red and white blood corpuscle picture had assumed normal values. The thrombocytes are still low as a residuum of the poisoning.

Simultaneously with the improvement in the blood picture increasing subjective improvement, and since the last examination has been allowed to begin other work.

Date	Hgb	Red bl. corp.	White bl. corp.	Thrombo-cytes	Differential leucocyte count					
					Ret.	Gran.	Lymph.	Eos.	Bas.	Mon.
16. 4. 40	49	1.8	800	23,000	0	24	64	4	0	8
18. 4. 40	49	1.8	900							
19. 4. 40	48	1.8	1100							
20. 4. 40	46	1.7	500		1					
21. 4. 40	49	2.3	900		2					
22. 4. 40	48	1.9	1000	17,000	1	26	64	0	0	10
23. 4. 40	52	2.6			2					
24. 4. 40	48	1.9	800		1					
25. 4. 40	48	2.4	1200		0					
27. 4. 40	49	2.5			1					
30. 4. 40	51	2.7	1200		6	43	48	2	1	6
3. 5. 40	51	2.5	1300		3					
8. 5. 40	32	1.5	1300		1	32	56	0	0	12
9. 5. 40	48	2.6			5					
11. 5. 40	49	2.6	1000		3					
14. 5. 40	51	2.8	1300	35,000	1	18	77	0	0	5
18. 5. 40	39	1.9			4					
20. 5. 40	39	1.9	1200		6					
22. 5. 40	59	2.8	1900		2					
27. 5. 40	59	2.6			4					
3. 6. 40	50	2.6	1300		16	24	63	3	0	10
8. 6. 40	50	2.4	1500							
13. 6. 40	53	2.4	1600		14	27	67	1	0	5
18. 6. 40	50	1.8								
22. 6. 40	56	2.5								
25. 6. 40	64	3.0		51,000	32					
28. 6. 40	67	3.2	2000	24,000	32					
5. 7. 40	75	3.7	1800	31,000	26	32	52	1	0	15
22. 7. 40	80	3.1	2500		13					
29. 7. 40	75	3.1	3800	31,000		39	52	1	0	8
11. 10. 40	83	3.5	1600	43,000		43	50	2	0	5
2. 12. 40	97	4.3	4000	52,000		71	25	0	0	4
17. 1. 41	94	4.5	5700	66,000		69	19	2	0	10

Repeated Arneth calculations showed a considerable shift to the left, which gradually decreased.

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Blood group determination of reticulocytes.

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It can be regarded as a recognised fact that the blood group differentiation in the human being begins as early as the embryo stage. The blood corpuscles in a 3—4-month-old foetus are carriers of agglutinin, and this property is, practically speaking, always complete in the new-born child. Another question which, according to the literature at present accessible to me, has not been gone into in more detail, is that of the time when the blood corpuscles, in the course of their development, get this blood group property. Probably the length of life of the corpuscles is relatively short, perhaps only 20 days, so that the organism is forced to be constantly forming new ones. We ask ourselves at what stage the agglutinin is developed in them. It is true that the way in which the erythrocytes arise is not yet known in detail, but an investigation of the immature forms, which can be differentiated microscopically, ought to lead to increased knowledge in this field, at any rate to some extent.

Thanks to developments in haematology, it has become possible to separate out immature red corpuscles under the microscope from fully developed ones. These immature forms, reticulocytes, appear in a certain percentage, usually under 1.0 %, in all healthy individuals. In those cases where, on account of loss of blood for example, an increased formation of new erythrocytes is to be reckoned with, the percentage of the young corpuscle forms is raised.

One of their characteristics is the possession of a nucleus-like structure which is vitally stainable. The reticulocytes differ somewhat from one another, so that attempts have been made to divide them into different groups. The commonest grouping is that made by Heilmeyer: group 0 comprises the nucleus-bearing erythrocytes, the normoblasts; group I the reticulocytes with a nucleus-like formation in the shape of a lump or a hobbin in the cell; group II reticulocytes with a distinct net with large meshes; group III with fragments of net, or full of rods and dots; group IV with small scattered dots most often situated in the periphery of the cell.

In an investigation of native blood, Fåhræus found a kind of peculiarly shaped corpuscles, which on account of their appearance he called 'hilus forms'. Gripwall later studied these cells in more detail, and their presence in hereditary haemolytic jaundice. As Gripwall points out, these cells have had no attention paid them hitherto because the morphological blood investigations usually take place with the aid of fixed and stained preparations, in which these cells do not appear. The first to mention these cells, albeit with extreme brevity, is Valentine. In his view, however, they are identical with the reticulocytes. The same result has also been reached by Åberg, and in the work I am now tendering, I support my assertions on the discoveries she made from an intensive investigation of this problem. It is true that the hilus forms observed by Fåhræus cannot be recognised in a fixed preparation, but according to Åberg a count of the reticulocytes in a preparation of this kind gives the same result as a count of reticulocytes and hilus forms inclusive in a moist, vitally stained preparation of the same blood. The hilus forms seem to be identical with the reticulocytes of groups I and II. Gripwall's drawing of hilus forms (p. 59) shows very well indeed that it is not only cells of group I which are characterised by uneven contours. Furthermore, Åberg has shown that the reticulocytes of group I remain outside the erythrocyte aggregate at the formation of rouleaux, in the same way as the hilus forms do.

In this connection it may also be stated that the 'knots' described by Boström are, probably are identical with the hilus forms.

The different reticulocyte groups are represented to different degrees in the healthy human being. The approximate quantity is shown in the calculation made by Trachtenberg and confirmed by Åberg (see Åberg for more details).

When a reticulocyte crisis sets in, the total number of reticulocytes is raised, and also the division into groups is changed. Forssell has shown that the youngest cells, groups I and II, are most numerously represented in those cases where the reticulocytosis reaches high values quickly, while groups III and IV predominate when the new formation takes place slowly.

Since the reticulocytes are so sparse in the blood of the healthy individual, tests for determining their blood group have to be made with blood from anaemic persons with a more or less pronounced reticulocyte crisis.

The staining and counting of the reticulocytes have been carried out according to the methods used by Åberg in her work, and I refer those interested to the technique she quotes.

For the agglutination test, blood is taken in the way given by Åberg, and mixed with the staining matter. An equally large drop of test serum is then added, and it and the blood drop well mixed with a glass rod. A fairly large coverglass is placed over the drop, and after 5—10 minutes the preparation is examined under an immersion lense. The erythrocytes are then as a rule more or less strongly agglutinated. The red corpuscles outside the corpuscle clumps or the aggregate are counted in the usual way, and the reticulocytes obtained from counting 1000 of these unagglutinated corpuscles. Preparations in which the red corpuscles are damaged (for example, taking the shape of a spiked club, or some such) are discarded.

A comparison between the different methods points to the smeared preparations giving a somewhat higher percentage figure for the reticulocytes than for the moist preparations. Probably, this is due to the reticulocytes of group IV not appearing as distinctly in moist preparations. The difference is very small and does not affect the final result. First-class test sera have always been used in the experiments — that is to say, the same as have been used in the daily practical blood group determinations.

The Material.

Case 1. The first patient whose blood was investigated suffered from pernicious bothriocephalus anaemia. (H_g 38/44, E. 1,672,000, L. 3,700). She belonged to blood group A and 35 % of her red corpuscles were reticulocytes. After the action of an anti-A serum, the percentage figure for the

reticulocytes among the non-agglutinated erythrocytes was 31.2. A repetition of the examination 2 days later gave a percentage figure of 20.5 after the usual reticulocyte count, and 19.6 after the action of anti-A-serum. The insignificant diminution in the percentage figure ought to fall within the limits for possible miscalculation. If the agglutination is very powerful, only a smallish number of erythrocytes remain outside the agglutination aggregate, and this must make the counting more difficult. In no circumstances is it possible to speak here of the reticulocytes not having been as agglutinable as the other erythrocytes. In this case, there was a slow increase of the reticulocytes. The first sample was taken at the top of the reticulocyte curve, the second somewhat later.

Case 2. The patient had the same diagnosis and the same clinical picture as the foregoing (Hg 30/35, E. 1,616,000, L. 2,200). The blood corpuscles had the properties OMN, and the experiments were carried out with anti—M and anti—N sera. The results were as follows:

- | | | | | | | |
|--------|---------------------|-------|-------------------|--------|-------|--------------------|
| 29. 1. | reticulocyte figure | 5.0 % | after addition of | anti-M | 6.0 % | and |
| | | | | » | » | » anti-N 5.0 %. |
| 13. 2. | » | » | 3.4 % | » | » | » anti-M 4.0 % and |
| | | | | » | » | » anti-N 3.5 %. |

It is not possible in this case, either, to speak of a dissimilarity between the agglutinability of the reticulocytes and the other erythrocytes respectively. In both the cases quoted here, the reticulocyte curve was at its peak or sinking, but the same result is also obtained when the sample is taken during the curve's rising phase, as was done in the following case.

Case 3. The patient had secondary anaemia and belonged to the blood group OMN (Hg 30/35, E. 3,056,000, L. 29,100). The test was performed in the usual manner, and the results were:

- | | | | | | | |
|--------|---------------------|--------|-------------------|--------|-------|---------------------------------|
| 28. 1. | reticulocyte figure | 11.7 % | after addition of | anti-M | 9.5 % | and |
| | | | | » | » | » anti-N 8.5 %. |
| 6. 3. | » | » | 20.7 % | » | » | » anti-N 20.8 % (the |
| | | | | | | test with anti-M was not made). |

The reticulocyte curve rose slowly in this third case, too. Thus the results of all hitherto reported investigations agree with one another, independent of whether the investigation was carried out during the rising phase of the reticulocyte curve, at its peak or during the sinking phase.

Divergent results were, however, obtained from further tests, this time made with blood from patients with the characteristic, quickly setting in reticulocyte crisis.

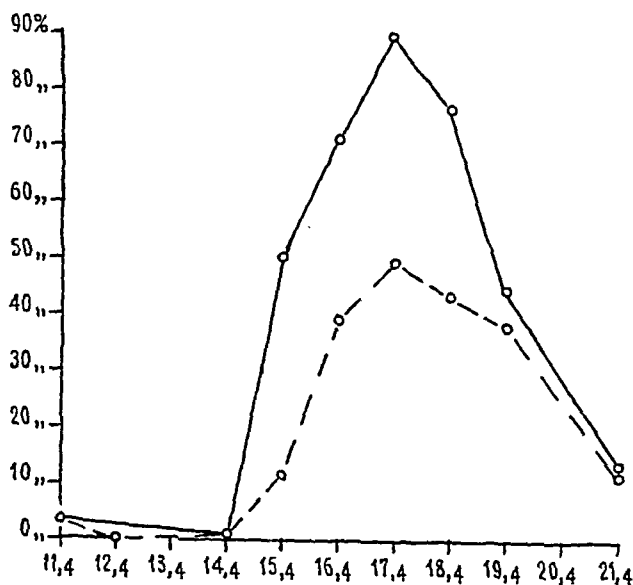
Case 4. The patient suffered from haemorrhagic anaemia resulting from gastric ulcer (Hg 22/26, E. 1,136,000, L. 5,700). At the height of the

crisis, the reticulocyte percentage in the blood was 32.5 %. The blood group was A. A new count following the action of anti-A-serum on the corpuscles gave the percentage figure 42.1. For the first time we have here an unquestionable difference between the two percentage figures, which, taking everything into consideration, cannot be regarded as falling within the limits for possible errors in counting.

Case 5. The same results, but with an even plainer difference, was obtained in another patient. Here, as with the previous one, there was a rapidly setting in reticulocyte crisis, following haemorrhagic anaemia (Hg 16/19, E. 1,640,000, L. 4,400). The patient's corpuscles had the properties OMN, and the test was made with anti-M and anti-N sera. The reticulocyte figure was 21.7 %, and rising after agglutination with anti-M serum to 51.8 %, and with anti-N serum to 37.5 %.

The investigations quoted above show a distinct dissimilarity in the results depending on whether the reticulocyte increase set in slowly or rapidly. To give a clearer picture of this problem, I am going to give further results from investigations, of several patients during the entire reticulocyte crisis, which were carried through without a break.

Case 6.¹ The patient suffered from ordinary pernicious anaemia and belonged to blood group B (Hg 31/36, E. 1,440,000, L. 4,500). Curve I shows the reticulocyte crisis observed.

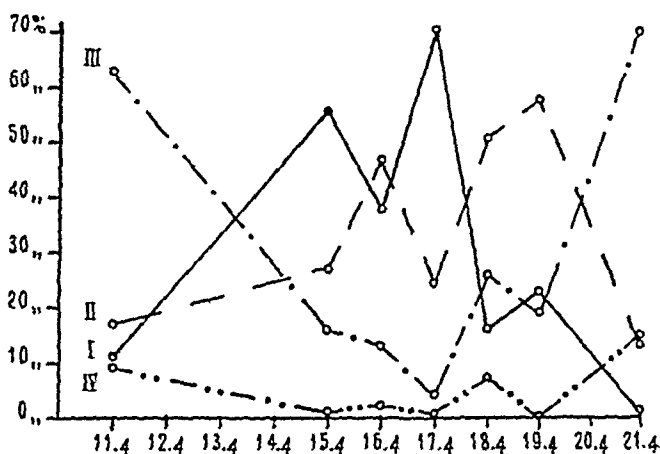


Curve I.

The date is shown by the abscissa and the reticulocyte percentage by the ordinate. The broken curve gives the reticulocyte per-

¹ Cases 6 and 7 are the same as those Åberg dealt with in her work. The case given in Åberg in curve I is identical with my Case 6.

centage in blood investigated in the ordinary manner, the unbroken line gives the percentage figure of reticulocytes of the non-agglutinated red corpuscles after an agglutinating anti-B serum had been administered. As the curve shows, the patient underwent a strong reticulocyte increase, setting in rapidly. In the beginning, and above all at the height of the crisis, the non-agglutinated corpuscles consisted largely of reticulocytes. The highest value was 89 %. Towards the end of the crisis, the reticulocytes seemed to become agglutinated to the same extent as the erythrocytes. This lastmentioned stage must no doubt be regarded as more or less answering the occasions when the crisis sets in slowly, in which case



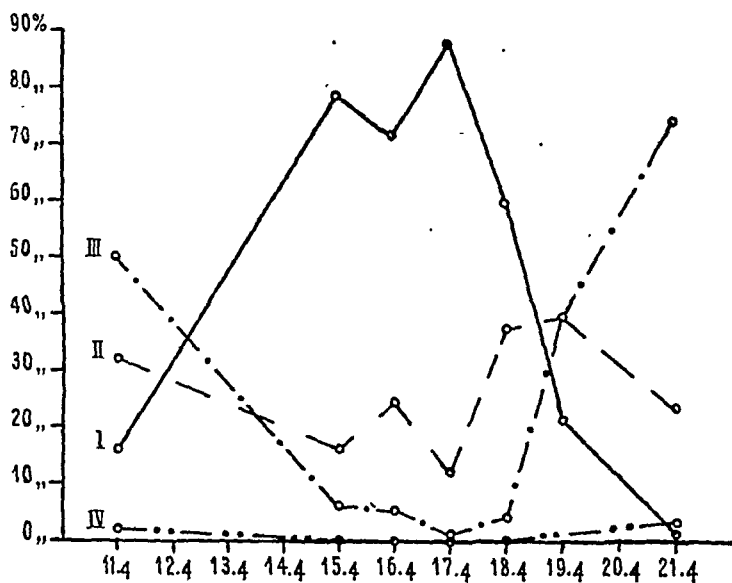
Curve II.

— according to experiments given here — non-agglutinable reticulocytes could not be observed. Everything speaks for the reticulocytes being agglutinable to different degrees during different phases of the crisis. Earlier investigations have already revealed that this is true of them from a morphological viewpoint (see Forssell for further details). To proceed in the direction now given, it is necessary to set about a differentiation of the reticulocytes in the four different groups mentioned earlier. Curve II gives the results of such a differentiation of the values shown by the broken line in Curve I — in other words, the reticulocytes counted in the customary fashion.

As was to be expected, the curve for reticulocytes from group I has risen during the start of the crisis and kept high during the climax, to sink practically to 0 when the crisis has passed off. The

curve for reticulocytes from group III show an opposite state of affairs, while the two other curves seen as a whole have the same course throughout the entire crisis. The slight irregularities all these four curves show are explained quite naturally when one takes into consideration how quickly the reticulocytes can vary in number from day to day, and remembers the difficulties bound up with the counting.

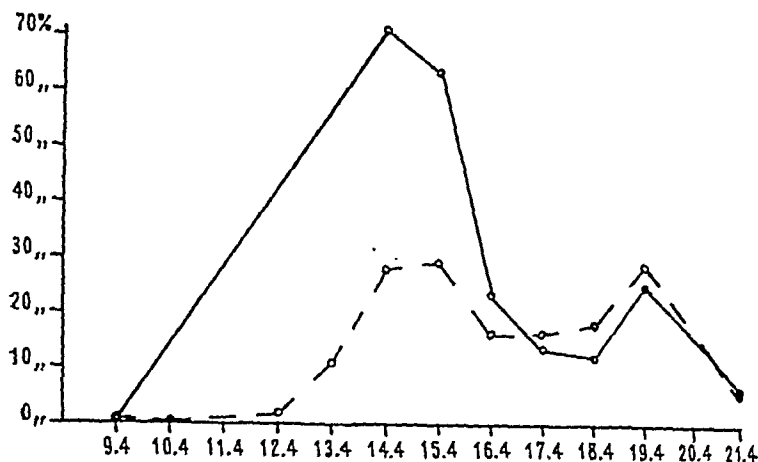
It is of great interest from the agglutination viewpoint to compare the results in the last-mentioned curve (II) with the corresponding differentiation of the non-agglutinable reticulocytes observed during the reticulocyte crisis (Curve III. Their total number can be read off from the unbroken line in Curve 1).



Curve III.

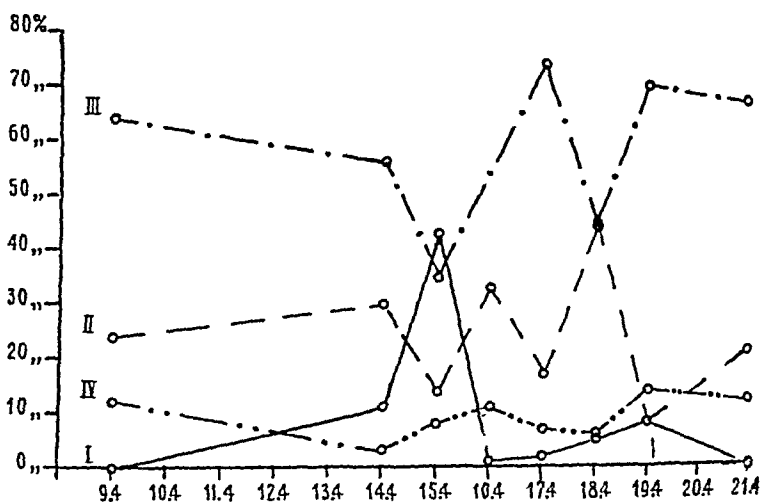
The results indicate that as long as non-agglutinated reticulocytes can be shown at all, they will be mainly from group I. It is primarily these, and to some extent, perhaps, the reticulocytes from group II also, which do not become agglutinated, and a comparison of the curves shows that a noticeable displacement in the differentiation results is obtained.

Case 7. Still another case may be quoted. The investigated patient had pernicious anaemia and belonged to the blood group B (Hg 30/35; E. 1,344,000, L. 7,200). Curve IV shows the reticulocyte crisis (the broken line) together with the percentage figure for reticulocytes after the action of an anti-B serum (the unbroken line).



Curve IV.

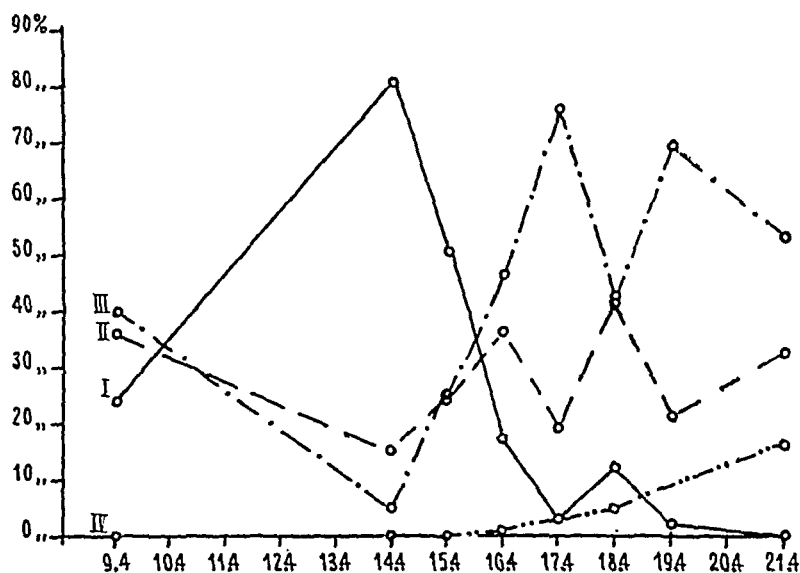
The fact that the patient was investigated for a rather longer period made a differentiation of the reticulocytes possible even after the plainly marked crisis was over. The results of the differentiations are shown by Curves V and VI, and agree with those obtained in the foregoing cases.



Curve V.

In this other case, too, non-agglutinated reticulocytes were observed only at the beginning and during the climax of the crisis. Further, they belonged mainly to group I.

The results discussed first in this paper indicate that only those reticulocytes remain unagglutinated which appear together with rapidly setting in crises while those attending a slow rise of the



Curve VI.

reticulocyte curve are agglutinated to the same extent as other erythrocytes. The two last-mentioned cases conform to this; the reticulocytes are not agglutinable as long as the reticulocyte curve rises steeply or has reached its highest point. In other words, we can say that non-agglutinable reticulocytes appear as long as the cells from group I predominate in number.

Judging from the results now put forward, we would say that the agglutinin is not completely developed in the reticulocytes from group I, while the immature corpuscles from groups III and IV are bearers of the property now in question. The reticulocytes from group II plainly have an intermediate position in that some of them clearly become agglutinated, while some remain unaffected. Thus it would seem that the point in time for the first appearance of the agglutinin in the red blood corpuscles is shown by my investigations. In this connection, I would refer to Åberg's observations on the relation of the different reticulocyte groups to one another from other points of view.

Earlier investigations (Fåhræus, Gripwall) have shown that reticulocytes from group I, or the hilus forms as the investigators mentioned call them, do not participate in the formation of rouleaux. While, by placing themselves side by side, the red corpuscles form typical rouleaux aggregates, the reticulocytes from group I remain

outside. For several reasons, the agglutination and the rouleaux formation ought to be looked upon as two separate phenomena (see Fåhræus, Schiff, Bergenhem, for further details), and therefore the reasons for the reticulocytes of group I not taking part in either the agglutination or the formation of rouleaux (the erythrocyte aggregation, according to Fåhræus) ought also to be of different natures. By repeating the experiment of Fåhræus and Bergenhem of increasing the corpuscles' tendency towards aggregation by means of warmth, it is furthermore possible to show that there actually is a difference between agglutination and aggregation. A sample with a high sedimentation rate is kept at 37 degrees of warmth till the sedimentation rate has gradually sunk to 0. During all this time, however, the corpuscles can be agglutinated with equal ease. At the end of the experiment, when the sedimentation rate is 0, the corpuscles display an equal power of absorbing isoagglutinin as before it started.

According to Gripwall, the veil in the so called veiled sediments (i. e., the boundary between the clear layer and the corpuscle column is more or less indistinct. Between them can be seen a cloudy layer, the veil.) consists to a great extent of hilus forms, or, according to Åberg, of reticulocytes from group I and group II respectively. Åberg has gone on with these investigations and carried out a differentiation of the immature cells inside the different parts of the veiled sediment. In her view, the veil contains chiefly reticulocytes from groups I and II, whereas these cells only appear sparsely in other parts of the blood column. This observation of hers has made it possible to get corpuscle emulsion, very rich in reticulocytes, for an ordinary blood group determination. One of the experiments belonging here comprises blood from a person belonging to blood group A. Blood was taken in the usual way from a patient with a distinct veiled sediment for the purpose of investigating the sedimentation rate of the erythrocytes (in 3.8 % sodium citrate solution). After standing two hours in the sedimentation tube, corpuscles were taken from the topmost part of the veil with a capillary tube. The reticulocyte percentage in this sample was 93. A differentiation showed that group I was present to 60 % and group II to 36 %, while the remaining 4 % was made up of group III. An anti-A serum had no effect whatsoever on these cells, while the corpuscles in the undermost part of the blood column in

the sedimentation tube became strongly agglutinated. This experiment, like those mentioned earlier in this paper, suggests that the agglutininogen has not been developed in the youngest reticulocytes.

The possibility should furthermore be noticed of the reticulocytes being able to bind agglutinin, even though they have not, judging by everything, been agglutinated. Thomsen's detailed investigations of leucocytes have given a result of this very kind, and based on this it can be said that the leucocytes actually are group-differentiated to the same extent as the erythrocytes. Best of all would be a corresponding testing of the reticulocytes, but external circumstances over which I have no control have up till now prevented me from carrying out such an one.

Summary.

By adding isoagglutinating human serum to a blood preparation stained supravitaly with brilliant cresyl blue, the agglutinability of the stained reticulocytes has been investigated. In so doing it was found.

that reticulocytes of group I were not, to judge by everything, affected by isoagglutinating sera,

that reticulocytes from group III and group IV were affected by isoagglutinating sera to the same extent as were mature erythrocytes, and

that reticulocytes from group II can, from the viewpoint of agglutination, most nearly be said to stand between these other groups, in that a part of the second group's reticulocytes may not become agglutinated, while part of them on the other hand do.

The above results can, in so far as they concern reticulocytes from groups I and II, be confirmed by an investigation of the cells in the so called veil in a veiled sediment.

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Reticulocyte ripening substances in human blood.

By

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It is well known that when freshly taken blood is stained with basic aniline dyes a more or less well pronounced network consisting of the so-called substantia granulo filamentosa appears in some of the erythrocytes. These cells are called *reticulocytes*. Among normal fully grown animals the number of reticulocytes varies from 0 to 30 per thousand of the total number of red blood corpuscles. In young animals and during the final foetal days a good many more are to be found.

Reticulocytes are regarded as young erythrocytes and are the only unripe cells that normally occur in the circulating blood.

Numerous investigations of the condition of reticulocytes in the vascular system under normal and pathological conditions are mentioned in literature, whereas only a few investigations are to be found regarding the physiological condition of reticulocytes and our knowledge of this is therefore strictly limited.

When blood is stored it appears that the reticulocytes slowly decrease in number. This circumstance was first demonstrated by Key (1921). In 1922 Pepper showed that when human or rabbit blood whose coagulation had been prevented by the addition of sodium citrate, was stored at body temperature, the number of reticulocytes declined rapidly in the course of three days, whereas it remained unchanged if the blood was stored at 4°. The same fact was demonstrated by Seyfahrt (1927). Heath & Daland (1930)

showed that the reticulocytes disappeared in the course of a few days if they were stored in vitro at 37° or injected into the pleural cavity of normal rabbits. They further demonstrated that the decrease in reticulocytes followed an exponential curve as is generally the case with every process due to ageing. They found the gradient of the curve to be different for rabbit blood and human blood but independent of the cause of the increased number of reticulocytes in the vascular system and this must be taken to imply that the reticulocytes when they appear, are of the same kind and only their ripening is dependent on the state of the surroundings.

These experiments with ripening reticulocytes have often been repeated both in vitro and in vivo but the figures given for the reticulocytes' length of life are very varied, since they swing from 24 to 144 hours; but in spite of this it can be said that all the experimenters agree that 1) reticulocytes ripen through various stages to normal 'grown' erythrocytes, 2) the process of ripening can take place in vitro, and 3) the ripening is dependent upon the storage temperature.

In the results of experiments (1942) previously mentioned, I have shown that the ripening of reticulocytes is conditional on the as yet unknown substances that are found both in plasma and in a number of the other organs of the organism. When the reticulocytes are washed in saline a very slow spontaneous ripening occurs; if liver extract is added to the saline or the reticulocytes are suspended in plasma, the ripening proceeds much faster.

These substances necessary for the development of the reticulocytes are found as already mentioned, in plasma and also in a number of organs but, strangely enough, the quantity is greatest in plasma. In a series of investigations (to be published) of various plasmata from a number of mammals, it appears that there is an interdependence between the quantity of reticulocytes in the circulating blood and the quantity of ripening substances in plasma so that species of animals with a low reticulocyte figure have a large quantity of ripening substances in their plasma whereas species of animals with a high reticulocyte figure only have a small quantity of ripening substances in their plasma.

As it would thus seem as if the quantity of reticulocytes in addition to the intensity of the erythropoiesis also depends on the plasma's content of ripening substances, a clinical investigation of

these facts will be of great importance. The present work deals with investigations concerning the ripening substances contained in normal human blood.

Technique.

Reticulocytes in rabbit blood were used, only males weighing from 2000—2500 grammes were used; they were kept singly and fed on turnips and cabbage leaves. When fed on hay, water must be given in addition. In order to obtain reasonable accuracy in counting the reticulocytes the animals were brought into a chronic anemic state through bleeding which is accompanied by considerable reticulocytosis. This was done by heart puncture or by bleeding from the ear into the Sjöwall apparatus (1936). 30—50 cm³ blood was taken daily.

After a week's treatment the animals' hemoglobin percentage was 40—50 and a red blood cell count yielded 2—3 millions per mm³ with 20—30 % reticulocytes. This state can be maintained for a month or more before the animals die.

In a ripening experiment 40 cm³ rabbit blood with at least 100 reticulocytes per mille was taken in 10 cm³ 3.8 % solution of sodium citrate. After scrupulous mixing, portions of 2.5 cm³ were put into 10 cm³ centrifuge tubes each containing 2—3 glass beads.

The blood must be mixed before each test in order to secure the same percentage of reticulocytes in each tube as reticulocytes sediment more slowly than mature erythrocytes. The tubes were then centrifuged for 5 minutes at 3—4000 revolutions a minute, the plasma sucked off, and the blood cells washed with 5 cm³ 0.9 % sodium chloride which was discarded after a second centrifugation.

The solution to be examined was then added to the washed erythrocytes, mixed for at least one minute and placed in 4 small test tubes with 2—3 glass beads in each. The test tubes were closed with rubber stoppers and numbered I—IV.

The reticulocyte percentage in Tube I was determined and once while the others were placed in a thermostat and rotated vertically at the rate of 30—35 revolutions a minute. Tube II was examined after 2 hours, Tube III after 4 and Tube IV after 6 hours incubation.

The clinical method of determining the number of reticulocytes is well known but our experience has shown the necessity for a very

careful technique and therefore we will go into the method in detail:

For staining *substantia granulo filamentosa* a solution of brilliant cresyl blue was used: 0.15 g brilliant cresyl blue in 100 cm³ 0.9 % NaCl. This solution was prepared in small quantities on account of possible changes in the stain solution (Cohen & Preissler 1930), and it was daily filtered before use.

The count of the reticulocytes was made in the following way: 2—3 glass beads and 0.5 cm³ of the solution of brilliant cresyl blue were placed in a small test tube. After mixing the blood to be tested for 1 minute (stopwatch), two or three drops of the blood were added to the stain solution, mixed, and kept for 20 minutes at room temperature. The contents of the tubes were then mixed for exactly 1 minute and a drop was placed on a slide and covered with a cover glass. The drop must be large enough to fill the entire space between the slide and the cover glass.

2 × 500 erythrocytes were counted at each count. As usual for counting a strong immersion lens and a good light were used so that even fine granules could be clearly seen.

Regarding the error in these determinations, we must refer to Marcussen's work on the distribution of reticulocytes (1938). As an example of why only rabbits with pronounced reticulocytosis were used for the experiments mentioned, it may be stated that:

1) According to the technique used in the experiments the count resulted as follows: 77/500—71/500, average $74/500 = 148 \text{ ‰}$, same preparation counted ten times: 72, 77, 71, 77, 70, 79, 74, 75, 73, 76, average 74.4 ± 2.76 calculated according to the formula:

$$m = \sqrt{\frac{\sum p^2}{n}}$$
 where p is the deviation from the average and n the number of counts.

2) The count of normal rabbit blood resulted in: 8/500—13/500, average $10.5/500 = 21 \text{ ‰}$; ten counts gave 9, 11, 14, 12, 8, 9, 9, 10, 8, 13, average 10.3 ± 2.21 .

These examples showed that while with the high reticulocyte figure there were only small variations (about $\pm 4 \%$), there was considerably greater variation ($\pm 20 \%$) with counts of normal rabbit blood.

The ripening process of reticulocytes under the conditions men-

tioned here follows the equation for the rate of monomolecular reaction:

$$K = \frac{1}{t} \log \frac{a}{a-x}$$

where t is the incubation time in hours, a the initial number of reticulocytes, and x the number of reticulocytes that developed during the experimental period concerned; the constant thus expresses the rate of the ripening.

Table 1.

Showing arrangement used and calculation of the results obtained.
Experimental rabbit No. 146.

	Erythrocytes washed in NaCl (0.9 %)	Erythrocytes washed in 0.9 % NaCl with Hepsol fortior 1 %	Erythrocytes washed in normal human plasma
	Percentage of reticulocytes	Percentage of reticulocytes	Percentage of reticulocytes
I. Before incubation	35.2	34.5	34.9
II. After 2 hours ..	33.8	30.7	31.8
III. After 4 hours ..	32.4	27.6	29.0
IV. After 6 hours ..	31.0	24.8	26.4
Percentage of loss			
II. After 2 hours ..	4	11	9
III. After 4 hours ..	8	20	17
IV. After 6 hours ..	12	28	24
$K = \frac{1}{t} \log \frac{a}{a-x}$			
II. After 2 hours ..	0.0089	0.0253	0.0204
III. After 4 hours ..	0.0090	0.0242	0.0202
IV. After 6 hours ..	0.0091	0.0238	0.0199
Average	$K_S = 0.0090$	$K_H = 0.0244$	$K_{Pl} = 0.0202$

Ripening constant for Hepsol fortior (190): $0.0244 \div 0.0090 = 0.0154$

Ripening constant for human plasma: $0.0202 \div 0.0090 = 0.0112$

Ripening index (corrected) for human plasma: $0.0112 : (0.0154 \cdot 0.97) = 0.76$

Table 1 shows the results of a single experiment carried out in the manner stated. As will be seen, the blood corpuscles that were washed in 0.9 % NaCl have a decidedly poor spontaneous ability to

ripen. The monomolecular constant corresponding to this is called K_s . If the blood corpuscles are washed in plasma the constant is called K_{pl} . As this expresses both the spontaneous ripening and the ripening produced by the added ripening substances, adjustments must be made for spontaneous ripening; the ripening constant for the plasma examined will thus be: $K = K_{pl} \div K_s$.

Since both the spontaneous ripening and the ripening of the reticulocytes induced by the ripening substances expressed by the monomolecular constant can vary considerably with the animals that furnish reticulocytes for the test, we must introduce a standard in order to compare similar results. As a standard we used hepsol fortior of a certain batch in a dilution of 1 %. The majority of others on the market being liver preparations, may also be used in suitable dilution as the standard. As oxen have no reticulocytes in their circulating blood and are the animals whose plasma contains most ripening substances, we thought that, assuming ox plasma to contain the maximum quantity of ripening substances, we were justified in choosing to take the content of ripening substances in ox plasma as the unit. *Ripening index: 1.00 indicates that the plasma or organic extract examined could ripen reticulocytes at the same rate as ox plasma tested opposite the same blood corpuscles.*

As the ripening constant K is proportional to the concentration of ripening substances this will consequently mean that a plasma sample having half the ripening constant of ox plasma will have a ripening index of 0.5 and so on. We fixed the standard of our ripening index opposite 11 different samples of ox plasma and found it averaged 0.97. The ripening index for a number of the other ordinary liver extracts used (Campolon, Extract. hepatitis »Gea«, Exhepa fortior pro inj.) was about the same. If one wishes to choose another standard it will be best to obtain a large quantity of the same preparation and determine its content in relation to that of ox plasma.

Since it appears that a number of amino acids are able to influence the ripening of reticulocytes, though to a lesser degree, we can use solutions of these instead of using ox plasma for fixing the standard even if the ripening index of amino acids is small and hence the accuracy of the count not so great. Whereas the rate of the ripening of the liver extracts investigated and the plasma concerned seems to be directly proportional to the content of ripening substances (Fig. 1), it does not seem to be the case were amino acids

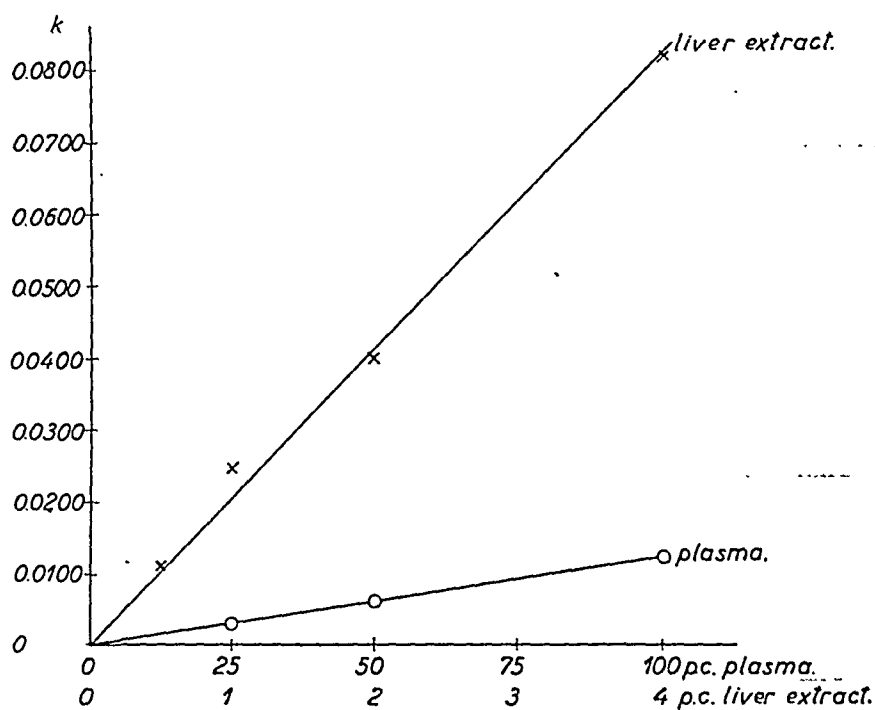


Fig. I. Dependences of constants on concentration of ripening substances.
 Abscissa: Concentration of ripening substances.
 Ordinate: Ripening constant.

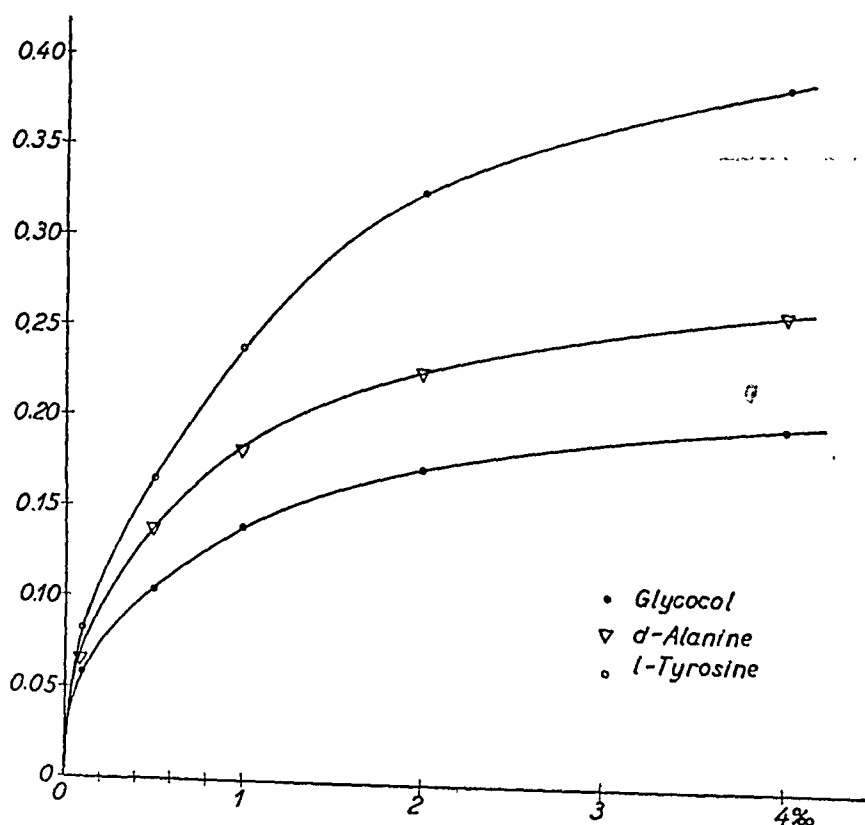


Fig. II shows the ripening index for various concentrations of amino acids.
 Abscissa: Concentration of amino acids.
 Ordinate: Ripening index.

Table 2.

Dependence of the ripening index upon the concentration of amino acids used.

	0.1 ‰	0.5 ‰	1.0 ‰	2.0 ‰	4.0 ‰
Glycocoll	0.056		0.136		0.193
	0.062				
	0.054	0.104	0.140	0.172	0.199
	0.058				
	0.058	0.104	0.138	0.172	0.196
d-Alanine	0.068	0.138	0.184	0.223	0.258
	0.062				
	0.066		0.177	0.229	
	0.065	0.138	0.181	0.226	0.258
l-Tyrosine	0.082	0.163	0.248	0.326	
	0.084				
	0.079		0.220		
	0.083				
	0.086	0.166	0.239	0.320	0.382
	0.082				
	0.082	0.165	0.236	0.323	0.382

are concerned (Fig. 2 and Table 2); there we see that the rate of ripening and with it also the ripening index do not rise proportionally with the concentration.

Judging from the investigations made it is advisable to use a 1 ‰ solution of tyrosine for fixing the standard; we found it had a ripening index of 0.24.

Results.

Through a number of examinations of plasma from various animals we found there appeared to be, as already mentioned, a certain agreement between the quantity of reticulocytes and the quantity of ripening substances, for a low reticulocyte figure cor-

responded to a high ripening index and a high reticulocyte figure corresponded to a low ripening index.¹

On the basis of these experiences we examined plasma from healthy human beings that from a hematological point of view did not present any clinical abnormalities. The blood samples were taken by puncturing the vein and here as in other experiments with plasma the coagulation of the blood was prevented by sodium citrate (3.8 %) in the proportion 1: 4; immediately after the samples had been taken they were centrifuged and the plasma sucked up for examination.

While the investigations with various species of animals showed somewhat constant conditions from animal to animal in the same group, it rapidly appeared that special considerations must be taken when investigating with human beings; for while investigations with men gave uniform results, those with women produced rather much variation. This proved to be due to the fact that at the beginning the menstruation cycle had been disregarded, for only in the middle between two periods of menstruation were values to be found corresponding to those found in men.

The result of the investigations may be seen in Table 3 and Fig. 2 where it appears that in human beings conditions similar to those in the animal kingdom are to be found, namely that a low reticulocyte figure goes with a high ripening index number.

Even if it is only a question of a small number of investigations (14 men and 7 women) we can say that there does not seem to be any difference in the ripening index for the different ages in spite of our finding a smaller quantity of reticulocytes among older people where the reticulocytes have furthermore a much 'older' appearance (Plum 1942).

As will be seen from Table 4 and Fig. 3 there is a rise in the ripening index corresponding to menstruation and at the same time a rise in the quantity of reticulocytes. This increase of the ripening substances in plasma takes place before menstruation and leads us to think that the regulation of the ripening substances is also governed by hormones.

Under various pathological conditions in human beings a rise

¹ The majority of the countings were worked out by Frk. Ida Milwertz and Frk. Else Johansen. I here accord them my thanks for their never failing interest and energy which considerably lightened my work.

Table 3.

Result of the hematological investigations made with 21 normal human beings and their reticulocyte ripening index numbers.

Age	Sex	Hemoglobin percentage	Erythrocytes in millions	No. of Leucocytes	Reticulocytes in thousands	Ripening index
24	♀	89	4.83	6340	4	0.77
25	♀	95	4.78	6120	3	0.76
27	♀	92	4.71	7040	3	0.79
28	♂	100	4.98	5640	3	0.78
30	♂	102	4.71	5860	4	0.77
32	♂	100	5.12	7260	4	0.77
32	♂	106	5.02	5280	6	0.72
32	♂	99	4.92	6140	5	0.76
32	♀	103	4.89	7220	2	0.81
33	♂	101	4.98	6200	2	0.80
33	♂	100	5.09	5840	3	0.78
36	♀	90	4.43	6420	3	0.79
38	♂	109	5.20	6880	4	0.76
48	♂	100	5.17	7460	2	0.82
61	♂	99	4.97	6360	3	0.76
69	♀	93	4.71	7480	2	0.80
73	♀	98	4.83	6240	1	0.84
76	♂	105	5.19	5860	2	0.79
80	♂	99	5.01	7220	1	0.85
81	♂	108	5.23	6280	3	0.77
82	♂	106	4.99	7280	2	0.81

in the number of reticulocytes has been observed. Reticulocytosis is generally regarded as a term for increased erythropoiesis. As the result of these investigations of the relation between the num-

Table 4.

Variation in the number of reticulocytes during the cycle of menstruation and the variation in the ripening index in a 27 year old woman.

Date	Menstruation	Number of reticulocytes in thousands	Ripening index
6—10—41	M. ads. 2nd day	8	0.92
13—10—41		5	0.79
27—10—41		3	0.76
3—11—41	M. ads. 2nd day	9	0.95
10—11—41		4	0.77
17—11—41		2	0.74
24—11—41		3	0.78
1—12—41		3	0.77
2—12—41	M. ads. 1st day	2	0.79
3—12—41		4	0.87
4—12—41		4	0.92
5—12—41		9	0.94
6—12—41		8	0.94
7—12—41		9	0.82
8—12—41		5	0.78
15—12—41		3	0.75

ber of reticulocytes and the quantity of ripening substances in normal human beings, we have, as already mentioned, seen that these two values are mutually dependent since a high figure for reticulocytes goes with a low concentration of ripening substances and vice versa. As the result of these observations we may conclude that reticulocytosis can be conditional upon two factors, namely as previously assumed 1) an increased erythropoiesis and 2) a reduction in the formation of ripening substances in the organism so that the cells ripen more slowly than normally. The conditions during menstruation when both the number of reticulocytes and the quantity of ripening substances rise, show however that the percentage of reticulocytes is not alone regulated by the quantity of ripening substances but that other circumstances also must contribute thereto.

Judging from these observations we must conclude that the percentage of reticulocytes can in certain cases express the ability of the organism to produce these as yet unknown substances that seem to

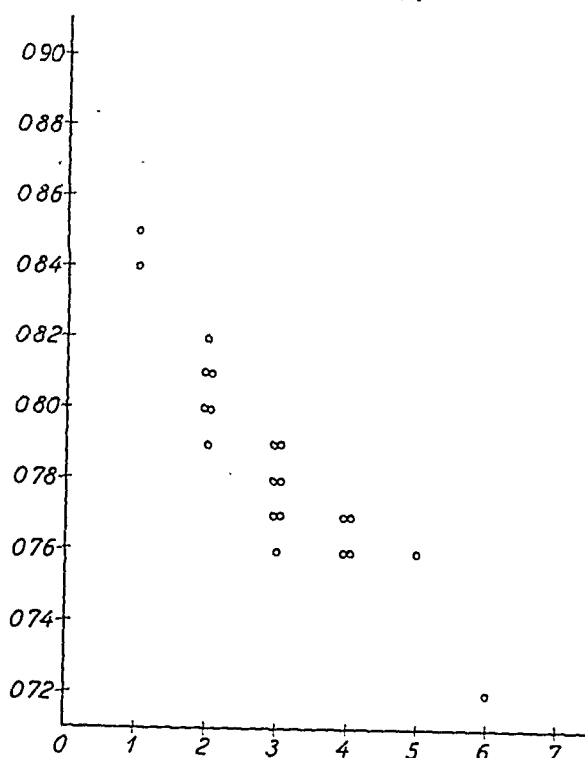


Fig. III. Variation in the ripening index and quantity of reticulocytes in 21 normal human beings.

Abscissa: Quantity of reticulocytes in thousands.

Ordinate: Ripening index.

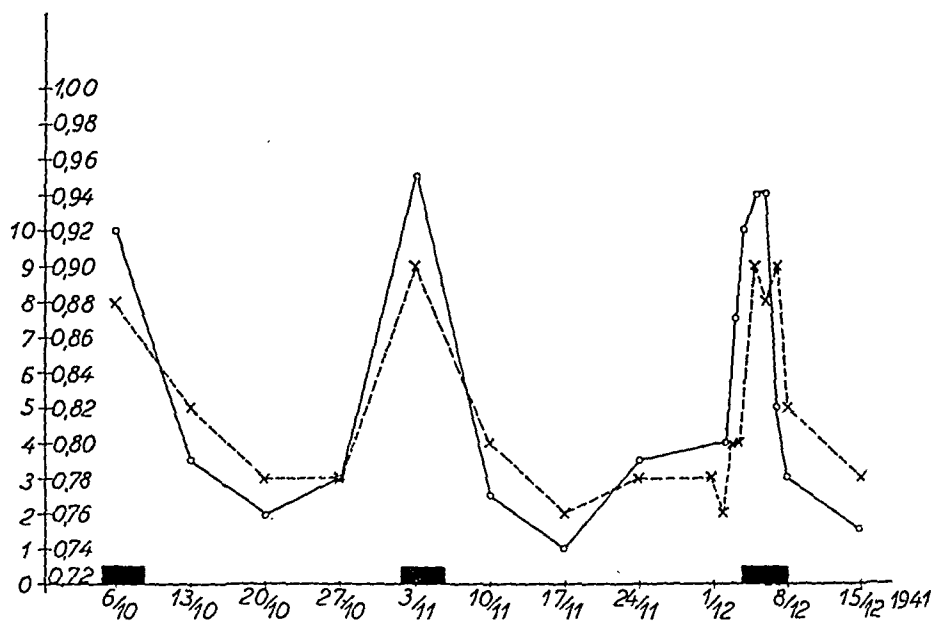


Fig. IV. Variation in the quantity of reticulocytes and the ripening index through three periods of menstruation in a 27 year old woman.

Abscissa: Time in days.

Ordinate: 0—0 Ripening index.

x—x Quantity of reticulocytes in thousands.

■: Menses adsunt.

play a part in the last link in the chain of the development of erythrocytes and thereby in the organism's regulation of the composition of the red blood, a circumstance which is now being clinically studied.

Summary.

Investigations regarding the ripening index of reticulocytes in human beings show, when consideration is taken of women's menstruation periods, that a low reticulocyte figure goes with a high ripening index figure; a circumstance which is moreover to be observed throughout the animal kingdom. Menstruation plays a big part in the height of the ripening index figure since immediately prior to menses a rise is seen in the as yet unknown substances that determine the ripening of the reticulocytes.

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Two cases of spontaneous hypoglycemia due to a tumor of the islands of Langerhans.

By

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The clinical symptoms due to overdosing with insulin were first described by Banting (1) et al. (1923). Shortly afterwards Seale Harris (2) suggested that similar symptoms might also be caused by hyperinsulinism, and the correctness of this view was confirmed by Wilder (3) et al. (1927) in a case of spontaneous hypoglycemia due to a carcinoma of the islands of Langerhans (in this paper from now on abbreviated to I. of L.) accompanied by metastatic nodules in the liver. In 1929 Howland (4) et al. reported that they had healed a female patient suffering from spontaneous hypoglycemia by the removal of a tumor of the I. of L. This operation has since been successfully repeated about fifty times.

Elsewhere we (5) have discussed the hypoglycemic symptomatology. Hypoglycemia proves to be a condition of comparatively frequent occurrence and is responsible for a wide range of symptoms that have often been ascribed to other causes, like epilepsy, brain tumor, hysteria, neurasthenia, gallbladder infection, duodenal ulcer etc.

Observations made by us on two cases of hyperinsulinism due to a tumor of the I. of L. seem interesting enough to justify their pub-

lication. One was a case of carcinoma of the I. of L. accompanied by metastatic nodules in the liver; it was found at autopsy. The other was of a young man suffering from a severe hypoglycemia, whose life was saved by the removal of an adenoma of the islet cells in the head of the pancreas.

I. A case of carcinoma of the I. of L. which was only recognized at the postmortem examination.

An obese woman, 52 years of age, was brought up for autopsy with the diagnosis: *insufficiencia cordis* and extrarenal uremia. In the head of the pancreas a greyish tumor the size of a chestnut was found, which had grown into the mesentery. The greatly enlarged liver weighed 4585 g, and consisted largely of light grey and yellowish globose nodules. The latter were necrotic in the centre, and those on the surface showed a central depression (fig. 1). The skin was not jaundiced; the sclerae were pale yellow. The macroscopical diagnosis was therefore: carcinoma in the head of the pancreas with multiple metastases to the liver. Thanks to the data contained in the paper of Wilder (3) et al. the microscopic examination led to the diagnosis: cancer of the islet cells of the pancreas. The primary focus in the pancreas contained, embedded in connective tissue, polygonal cells with chromatinic round to ovoid nuclei of different size, but reminding one nevertheless of normal islet cells (fig. 2). Mitoses were found sporadically. A great many areas were necrotic. In a few veins tumor cells were seen. Outside the tumor the pancreas was practically normal.

The tissue that had proliferated into the mesentery was analogous to that described above. The contact with the circulation was here very close indeed, for tumor cells were found immediately against the walls of the capillaries.

The metastases in the liver showed a more polymorphic character than the primary focus, and mitoses were far more numerous. The tumor cells often lay embedded like islets in a strongly developed stroma of connective tissue (fig. 3). They were also found at several places in the capillaries in the midst of liver cells showing to a marked degree fatty degeneration (fig. 4). The bile tubules occasionally contained bile cylinders.



Fig. 1. Left: primary carcinoma in the head of the pancreas. D = duodenum. Right: metastatic nodules occupying the larger part of the greatly enlarged liver. The centre of these nodules is necrotic and those on the surface show a central depression.

As the diagnosis cancer of the I. of L. was only made after the data of the microscopical assay had become available, it was too late to determine the amount of insulin contained in focus and metastases. Of cancer of the I. of L. accompanied by metastatic nodules in the liver seven cases have been reported, and they all showed microscopically the same character as that described above. In three of them an extract was made, either from the focus or from the metastases, and this, injected into rabbits, was found to lower the blood sugar concentration [Wilder (3) et al., Bickel (6) et al., Cragg (7) et al.]. In four cases during the life of the patients the symptoms of spontaneous hypoglycemia had been noticeable [Wilder (3) et al., Judd (8) et al., Cragg (7) et al., Joachim and Banowitch (9)]. Tumors starting from endocrinous glands are preeminently remarkable for their specific function [Askanazy (10)].

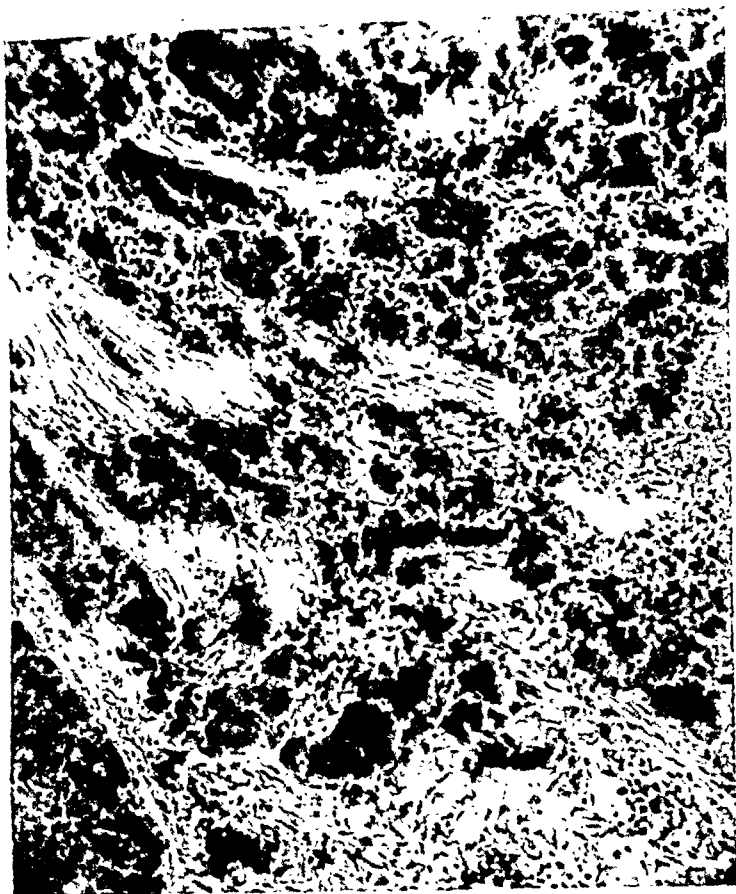


Fig. 2. Primary focus in the pancreas consisting of polygonal cells provided with chromatinic round to ovoid nuclei embedded in connective tissue. On the right side necrosis is visible. (100 x).

Our patient was ill for eight weeks. She suffered from attacks of pain radiating from the upper right part of the abdomen to the back and to the right shoulder. She was neither feverish nor jaundiced, but vomited often. She also felt dull and sleepy. Although neither sugar nor proteins were found in the urine, a coma uraemicum or diabeticum was expected, and she was therefore taken to the Academic Hospital, Leyden. The examination of the abdomen was hindered by the strongly developed panniculus adiposus; distinct aberrations were not found. The urine contained much urobilin, but no reducing substances. On account of the serious attacks of vomiting, the amount of chlorine in the blood was determined; it was found to be low (2.13 g per litre in toto; 2.98 g per litre in the blood plasma; 1.34 g per litre in the erythrocytes). As the ureum concentration of the blood was 840 mg per litre, an uremia »par manque

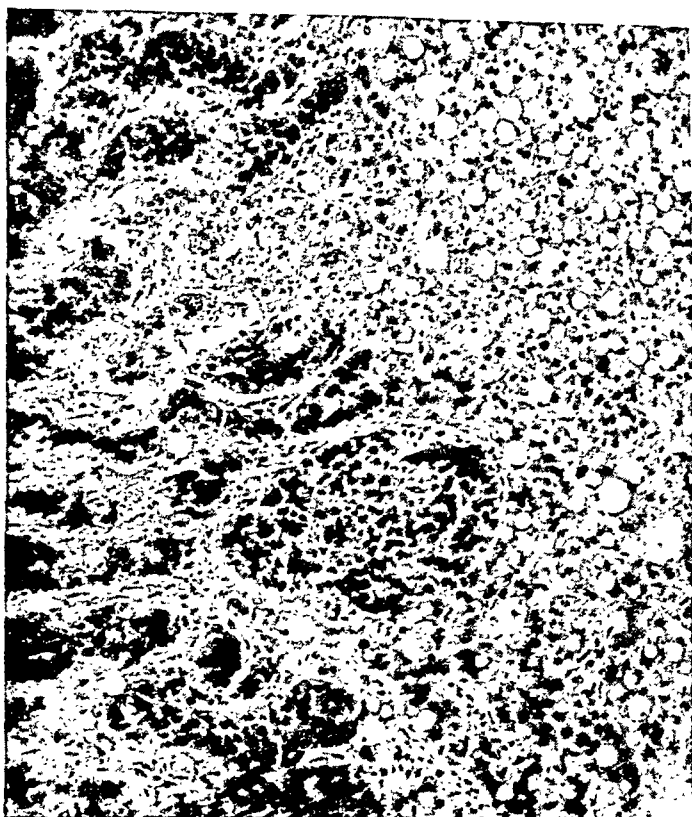


Fig. 3. Metastatic nodule in the liver showing an unmistakable resemblance with normal I. of L. The liver parenchyma (to the right) shows a high degree of fatty degeneration. (100 x).

de sel» was supposed to be present. Even though large amounts of NaCl were given, per os as well as intravenously, the patient grew worse. She became slightly jaundiced, and the reaction of Hymans van den Bergh proved directly positive and indirectly increased: 4.29 U. As the urine showed a slight reduction¹, the blood sugar concentration was determined: 112 mg %. Unfortunately the time at which this determination was made, was not noted, so that it is of no use. Nine days after her entry the patient died, practically in coma. Spontaneous hypoglycemia was not taken into considera-

¹ Wilder (3) too has observed that in cases of hyperinsulinism the urine may temporarily show reduction. This reduction may be due to the presence of dextrose, and if so, then it can be accounted for by assuming that the great number of metastases impede the normal function of the liver to such a degree that part of the carbohydrates of the food can no longer be stored in the form of glycogen, but are temporarily passed on to the blood and the urine.

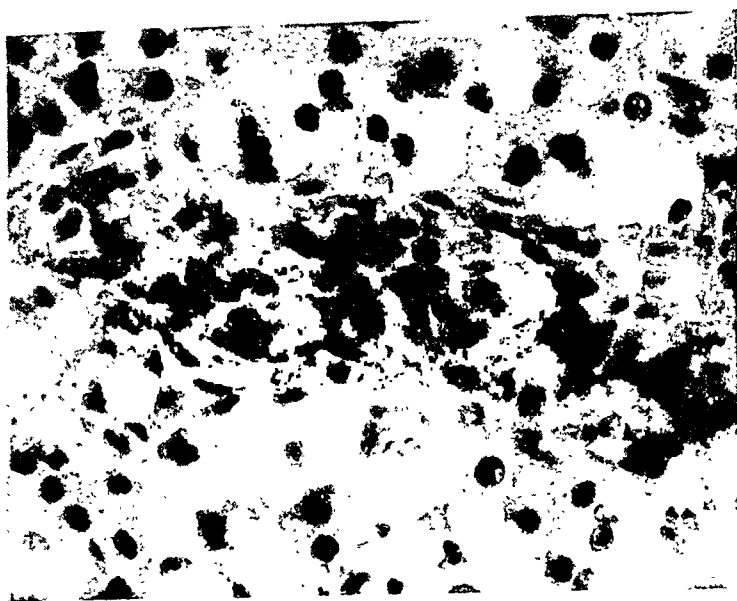


Fig. 4. A capillary in the midst of liver cells showing fatty degeneration; the capillary contains tumor cells.

tion, but now that the microscopical assay has suggested its presence, the clinical aspect of the case is comprehensible enough, for the abdominal pain as well as the vomiting and dullness and, finally, the coma, all fit into the syndrome of hypoglycemia.

II. A patient suffering from an adenoma of the I of L., who was successfully operated.

D. L., a 18 year old industrial labourer, came in October 1940 to the outpatient department of neurology, Leyden. He complained that faintness had overcome him on his bicycle. A few minutes earlier he had become aware that his thoughts were wandering, and that, as in a dream, reminiscences passed through him. He grew chilly, began to shiver with cold, and his legs felt tired and heavy. The patient did not perspire. Notwithstanding his illness, he rode home. After he had eaten a slice of bread, he felt better. Four months earlier he had had a similar attack, when at the factory. There he seems to have lain kicking his legs (but without biting his tongue and without incontinentia urinae et alvi).

At home too he had had several similar attacks; he then talked aloud without knowing what he was saying, and afterwards dropp-

ed asleep. The practitioner who treated him, could not explain these attacks of »syncope». The patient thought there was some connection between his complaints and the outbreak of war.

At first the patient was treated for atypical genuine epilepsy. Examination, however, revealed nothing which might have accounted for an organic brain disease. The photograph of the skull revealed no aberrations. In spite of the administration of luminal, the complaints did not quite stop. He still felt somewhat tremulous, and once he had another attack, which he ascribed to an insufficient meal. A cup of hot coffee revived him.

In April 1941 the patient returned to the outpatient department of neurology. His appearance was absolutely that of a man being intoxicated and he was in a state of subcoma. The possibility of a spontaneous hypoglycemia was taken into consideration (Dr. W. F. Storm). The blood sugar concentration indeed proved to be only 45 mg %. After sugar had been administered, the patient recovered completely. For further observation he was taken to the internist's ward. Physical examination revealed no aberrations, nor could resisting parts be palpated in the abdomen. Liver and spleen were not enlarged. The blood pressure was 134 mm Hg. systolic, and 88 mm Hg. diastolic. Pulse: 80, regular and equal. In the urine no abnormal components were found; the reaction on urobilinogen was negative. The precipitation rate was in the first hour 2 mm, in the second 4 mm (method of Westergren). The Wassermann reaction was negative. The bilirubin reaction after Hymans van den Bergh was normal. The blood sugar concentration, the diet being normal, was originally:

8^h.30: 52 mg % (fasting); 11^h.30: 54 mg %; 3^h.30: 70 mg %.

From the numerous sugar determinations made of the blood of the patient in the period of his illness before the operation, it appeared in the first place that the fasting values were constantly subnormal (average 48 mg %); and in the second place that these values, notwithstanding the large amount of dextrose that was daily administered, were decreasing.

As there was no indication of hypofunction of the anterior lobe of the hypophysis, the thyroid or the adrenal glands, we diagnosed: probably an adenoma of the I. of L., and an operation was decided on. As spontaneous hypoglycemia may lead to sudden death, permanent psychical changes or a malignant degeneration of a perhaps

innocuous tumor of the I. of L., we warned against a conservative therapy.

The patient was operated under nitrous oxide-oxygen-aether narcosis (Kooreman). An hour previous to the operation he was given 100 cm³ of a 25 % dextrose solution intravenously, and shortly before the operation a permanent intravenous infusion of Ringer's solution containing 5 % dextrose was attached. The abdomen was opened with a median longitudinal incision above the umbilicus. The ligamentum gastro-colicum was divided over a great distance. The stomach was drawn upwards and the transverse colon downwards, corpus and cauda of the pancreas thus coming into full view. The pancreas looked perfectly normal, but on palpation there proved to be two sharply defined, resisting sclerioses, one near the upper margin and one in the centre of the corpus, both slightly protruding. They were about $\frac{1}{2}$ —1 cm in diameter. Although their colour was not markedly different from the remaining part of the pancreas, they were taken for adenomas of the I. of L., and removed. The two wounds in the pancreas were sown up with fine silken thread, and the pancreas bed drained. The ligamentum gastro-colicum and the abdomen were then closed.

Previous to the dextrose administration the blood sugar value had been 80 mg %; after the operation it was 83 mg % (the permanent intravenous infusion remained in function after the operation); four hours later 102 mg %. In spite of the intravenous infusion, the increase of the blood sugar value was therefore very limited. This made it seem doubtful that we should have succeeded in removing the adenoma. In the evening the blood sugar value decreased to 75 mg %. The next day the intravenous infusion was removed. The blood sugar value then decreased to 45 mg %. Two days later in the early morning the patient had an attack of hypoglycemia, from which he could only be roused by the administration of dextrose. Histological examination of a part of the removed tissue did not reveal any pathologic changes. This excluded the possibility of a diffuse hypertrophy of the I. of L. The amount of insulin in what remained of the extirpated part of the pancreas was about 2 U. per gram tissue (Overbeek, Pharmacological Laboratory, Leyden). The wound healed without complications and after 14 days the patient was removed to the internist's ward. A dextrose tolerance test was made. Determinations in the morning, before

food had been taken, could not be made, as the patient would have fallen into coma. At 6 o'clock in the morning the patient therefore had a light breakfast, and at 9^h.30 a blood sample was taken for the assay; the value proved to be 44 mg %. Then the patient was given 50 g dextrose per os; after that the blood sugar values were: 10^h: 108 mg %; 10^h.30: 127 mg %; 11^h: 78 mg %; 11^h.30: 74 mg %; 15^h.30: 76 mg % (cf. fig. 5). The blood sugar values were also determined when the dextrose was not given per os, but intravenously, the injection consisting of 100 cm³ of a 20 % dextrose solution. This series of determinations was repeated after the patient had received 1 cm³ Benerva forte daily for 6 days. The level of this curve proved to be higher (cf. fig. 5).

In spite of the low blood sugar values (down to 20 mg %) the patient did not become unconscious.

The liver function was estimated with the aid of the galactose test; it proved to be negative. The urine did not contain urobilin.

As the symptoms might be due to an atypical attack of tetany, the calcium and phosphor concentrations of the blood were determined; they were found to be 10.3 and 5.2 mg % respectively, which excludes this possibility.

Although dextrose was given regularly, the attacks of hypoglycemia continued. In view of the dangerous complications of the spontaneous hypoglycemia, another operation was decided on. The results of our further investigations had changed nothing in our original diagnosis; on the contrary our conviction that a tumor of the I. of L. must be present, was firmer than before.

Eight weeks after the first operation the second one was made (Kooreman). The patient's weight had in the meantime distinctly increased, and the operation was therefore more difficult. This increase in weight has often been reported and is doubtless due to the diet being rich in carbohydrates and to the administration of extra dextrose. The operation was prepared in the same way as the previous one. The same entrance to the pancreas was used. Then it proved necessary to make a further incision perpendicular to the median one and to the left of it. Many adhesions were found between the front part of the stomach and of the colon with the wall of the abdomen. Moreover, a large part of the bursa omentalis proved to be obliterated. After some trouble a good view of the pan-

creas was obtained. The corpus and cauda and, as far as possible, the caput too were carefully examined, but an adenoma could not be found. Then corpus and cauda were mobilized, and carefully palpated, but without result. It was decided to remove a large part of the pancreas in the hope that in this way an unpalpable adenoma might be got rid of. The possibility that a diffuse hypertrophy of the I. of L. might be present, was disproved by the results of the histological examination and of the insulin determination made after the first operation. The mistake we made at the second operation, will be discussed later. It appeared necessary to extirpate not only a part of the pancreas but also the enlarged spleen. This, the cauda of the pancreas and that portion of the corpus which extended to the left of the large vessels were removed at the same time. The pancreas wound was carefully sown up with silk, catgut being unsuitable as it is digested by the pancreatic juice. Then the pancreas bed was drained. Whipple (11) too is of opinion that splenectomy is necessary in order to prevent serious hemorrhagiae, which might easily come to pass when corpus and cauda of the pancreas are divided from the spleen vessels. Of the liver too a small part was removed for the determination of the glycogen concentration (Overbeek). It proved to be 1.08 g % (during the operation too the patient still received dextrose!). The normal glycogen concentration in the liver is about 6—8 g %. The liver showed no pathological changes.

This operation too proved to be unfortunately unsuccessful. Immediately after the operation the blood sugar value was 110 mg %; 4 hours later 108 mg %. Then it went down gradually. After two days the dextrose infusion was removed, and the day after the patient had another attack of hypoglycemia. The histological examination of the extirpated part of the pancreas showed no abnormalities, and an adenoma could not be found.

This time too the wound healed without complications, and four weeks after the operation the patient was removed again to the internist's ward. Here some of the clinical investigations were repeated. Quick's hippuric acid test was normal; the galactose test again showed no diversion. According to the Röntgenologist the Röntgenogram of the duodenum suggested the presence of a tumor in the head of the pancreas, as there was a relatively large bend in the duodenum. Afterwards this proved to have been more or less acci-

dental, as the tumor brought to light by the third operation was very small.

The patient were given adrenalin injections, about 2—4 cm³ of a 1: 1000 solution daily. The amount of sugar required by the patient was now much smaller. On some days even he received no extra dextrose at all. But the high adrenalin doses which he received during one week (3 dd. 2 cm³), could not prevent occasional attacks of hypoglycemia.

We found the following blood sugar values (cf. fig. 5): fasting 38 mg %; after two injections, each of 2 cm³ of a 1: 1000 adrenalin solution, an increase to 66 mg %. The condition of the patient, who had been in a state of subcoma, was at the same time considerably improved.

The large and more or less constant supply of insulin produced in these patients by the tumor of the I. of L., results finally in a decrease of the amount of glycogen stored in the liver. So it is explained that during the second operation, even though the patient was supplied with a dextrose infusion, the amount of glycogen was but 1.08 g %. The adrenalin injections lower this amount still further. When an operation is contra-indicated, and also where a symptomatic therapy is desirable, the adrenalin administration should therefore be combined with gifts of dextrose.

The diagnosis, organic hypoglycemia due to a tumor of the I. of L. was for our patient maintained: the fasting blood sugar value was regularly low, the liver function normal, and the dextrose tolerance tests and the progressive character of the disease pointed in the same direction. When the patient received no extra sugar, he was now in the morning usually unconscious. In view of these facts and taking into account the dangerous consequences of spontaneous hypoglycemia, particularly should the patient be nursed at home, we were bound to advice another operation. Especially as Whipple (11) and Windfeld (12) had successfully removed adenomas from the head of the pancreas, and as we were convinced that in our patient too the adenoma must be present in that part of the organ, we considered a third operation highly desirable and, in fact, the patient's only chance of life.

Ten weeks after the second operation the third one was performed (Kooreman). To prepare the patient for the operation, he received a permanent intravenous infusion of Ringer's solution, this

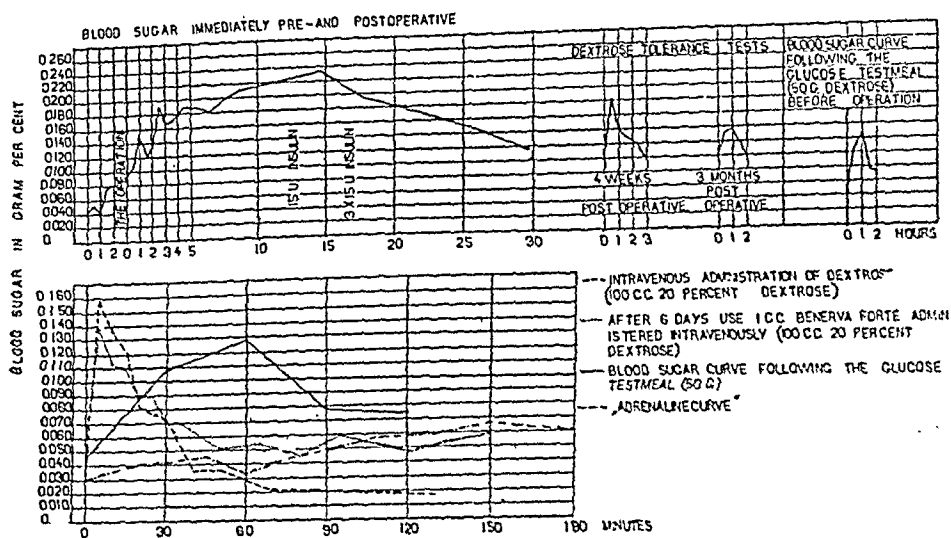


Fig. 5. For the explanation compare the text.

time without dextrose. During the operation moreover a dose of 5 g dextrose was intravenously injected. To enter into the body cavity the wave incision (Kehr) was used. After the removal of many adhesions the duodenum could be mobilized according to Kocher's method. Then the caput pancreatis was painstakingly searched. Its aspect was normal, but below the papilla of Vater an elastic tumor about the size of a small hazel-nut was palpated. After a great deal of trouble due to the various bloodvessels, we succeeded in removing this tumor, which appeared to be of a blue-purple colour, and to be surrounded by a capsule. No other tumors were found. After the bleeding had carefully been checked, the wound was closed, and the operation bed drained. The lengthy operation was well sustained by the patient. This time is proved to be successful. Half an hour after the operation the blood sugar value was 105 mg %; the other values obtained during the first 24 hours after the operation are given in fig. 5 in the form of a curve, and will be discussed below. The next morning already it appeared that administration of extra dextrose was no longer necessary, and that instead insulin had to be given. Owing to a slight infection, the wound did not heal so well as before. After a few weeks the patient went home completely cured. Controls, three and eight months later, showed a perfectly normal blood sugar curve. The patient had no complaints, and had resumed his work at the factory.

Pathological Report.

Gross Examination.

The tumor is slightly smaller than a hazelnut, shows a wine-red tinge and a rubber-like consistency, and is enclosed in a thin capsule of vascularized connective tissue. The section is purple-red and minutely granulate. As part of the tumor was destined for tissue culture, the whole object had to be removed and divided aseptically, which made measuring and weighing impossible, but as the part destined for microscopical investigation was about one third of the tumor, and as it weighed 370 mg, we may conclude that the weight of the whole tumor must have been about 1.1 g.

Microscopic Examination.

The tissue is strongly vascularized, hyperemical and shows in several areas extravasation of blood. From the thin capsule vascularized septs of connective tissue penetrate between the tumor cells. These are round or polygonal, and provided with a round or ovoid nucleus, showing a delicate tracing of chromatin. The protoplasm stains evenly, and is not vacuolated; and as it does not accumulate Sudan III, fats and lipoids are absent.

Where the tumor cells abut on the septs of connective tissue they often assume a cylindrical shape, and arrange themselves in the form of trabeculae. Not unfrequently they appear like islets resembling the I. of L. There is no polymorphism, and there are no mitoses (fig. 6 and 7). There are also cells with very little protoplasm and a pycnotic nucleus, which are not unlike lymphocytes, though slightly larger. They occur in nests that are strewn throughout the section. Hyalinization is not shown by the connective tissue, neither in- nor outside the tumor, and the amyloid tests are negative.

In the capsule tumor cells are found locally. In several of the smaller veins too they lie in the midst of the erythro- and leucocytes (fig. 8). Does this mean that a dissemination to the liver already had taken place? Or was the presence of the tumor cells in the vessels due to the manipulations to which the organ in the course of this rather difficult operation had been subjected? As the tissue showed in several places extravasations of blood, the last-named

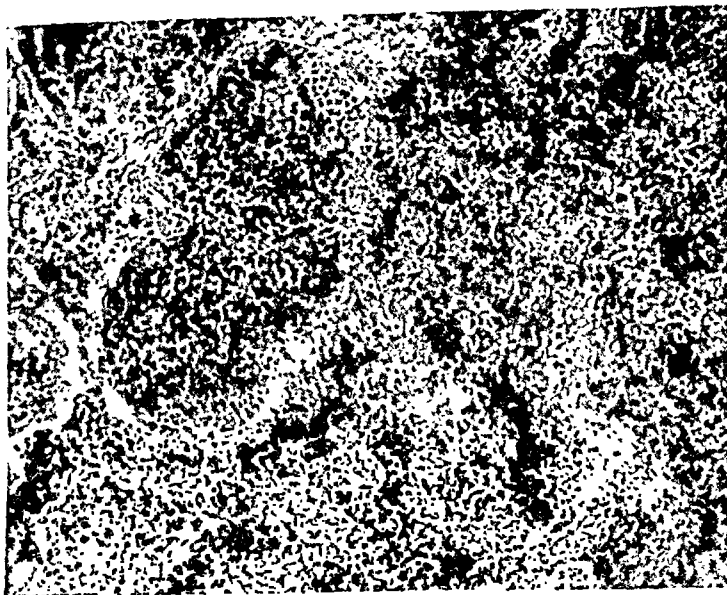


Fig. 6. Adenoma cells resembling normal islet cells. (100 x)

supposition is probably the most acceptable, but the first possibility is not excluded. The proliferation into the capsule as well as the presence of tumor cells in the circulation are, however, a warning against too great optimism with regard to the prognosis: If after five years the patient should still be free of complaints, it may be taken for granted that the presence of tumor cells in the circulation was a by-effect of the operation, but if the patient should die of metastatic nodules, then it will be impossible to decide whether the dissemination had taken place before or during the operation. In any case at the time of the operation the liver showed no trace of metastatic nodules, and a lymph gland removed from the neighbourhood of the pancreas proved, when examined under the microscope, to be free of tumor cells.

As there is no atypia, but on the contrary a striking resemblance with the cells of the normal I. of L., no polymorphism and no mitoses, it seems better not to classify this tumor as a carcinoma, but as an adenoma.

Virginia Frantz (13), dealing with 18 adenomas, observed a local proliferation into the capsule and the presence of tumor cells in the circulation four times. Of these four patients one after the operation died of bronchopneumonia, whereas the three others were respectively 17, 13 and 5 months after the operation still per-

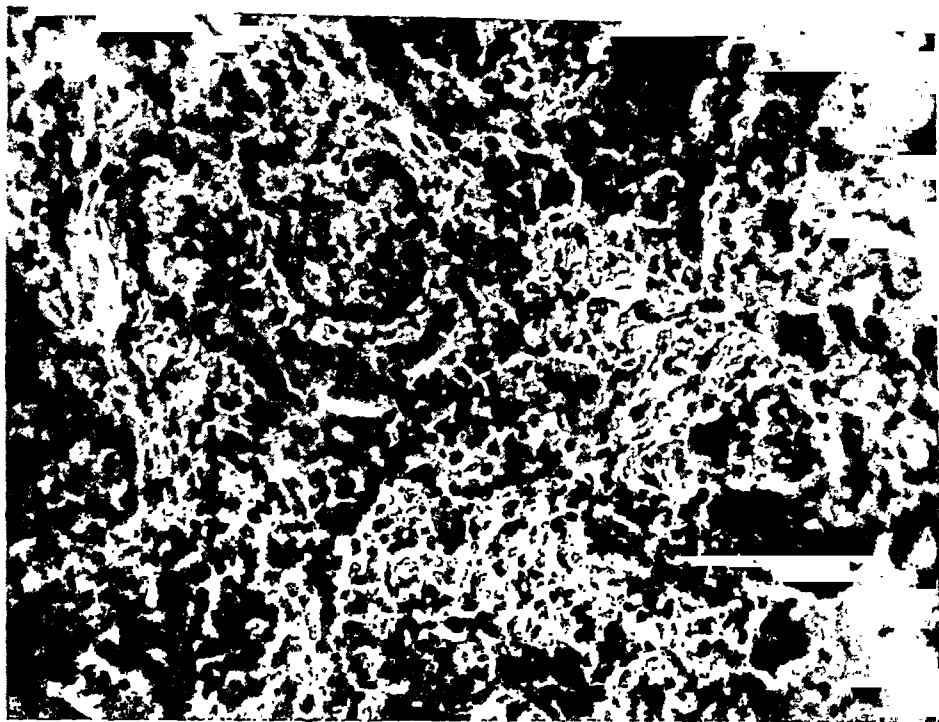


Fig. 7. Trabecular structure of tumor cells abutting on the connective-tissue septa. (200 x).

fectly free from complaints. We agree with this author, by whom these tumors are designated as malignant adenomas that with regard to the prognosis it will be necessary to keep these patients under observation. Should a relapse occur, it should be reported.

The proliferation into the capsule, and sometimes even further, has been observed by other investigators also (a. o. Priesel (14) Thalhimer and Murphy (15), Howland (4) et al., Bast (16) et al., Munakata (17)]. In tumors arising in the endocrinous glands it is, however, often as difficult to draw the line between an adenoma and a carcinoma, as between an adenoma and a hyperplasia.

The patient described by Howland (4) et al. was 10 years after the removal of a carcinoma (in our opinion a malignant? adenoma) of the I. of L. in excellent health, and may therefore be regarded as cured [cf. Campbell (18) et al.).

True carcinomas of the I. of L., with polymorphism, mitoses, necrosis and metastatic nodules, have but seldom be described. We found but 7 records [Wilder (3) et al., Hamdi (19), Judd (8)

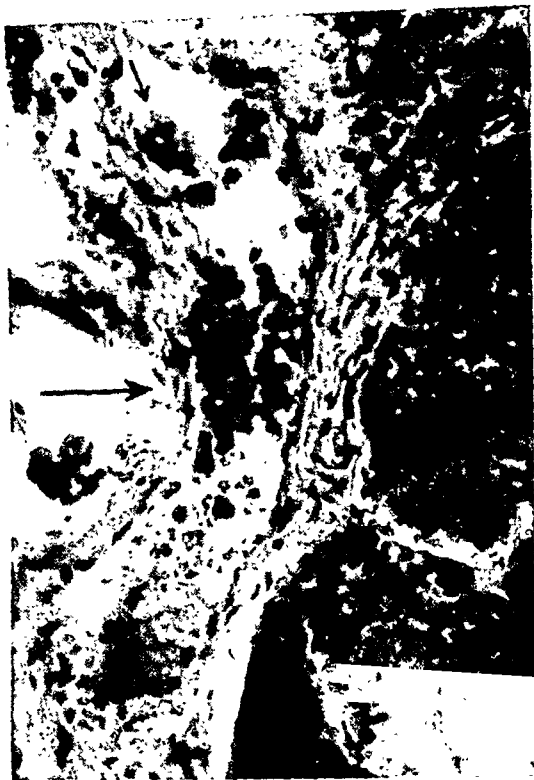


Fig. 8. A small vein in which, besides red and white blood corpuscles, tumor cells are present. (200 x).

et al., Evangelisti (20), Bickel (6) et al., Cragg (7) et al., Joachim and Banowitch (9)], and ours therefore is the eighth. Possibly this syndrome too is still insufficiently acknowledged.

Discussion.

As a more or less detailed survey of the literature dealing with this interesting syndrome has already been given by others (cf. especially Whipple and Frantz (21) and Frantz (13), we will mention a few points only.

A paper by Conn (22) gives an excellent review of the various causes of the hypoglycemic syndrome, and sharply discriminates between the organic and the functional form. A detailed differentiation is necessary, as the therapy should, as far as possible, take the underlying cause into account. Elsewhere we (5) have already discussed the importance of Conn's paper. The fasting blood sugar

value, the dextrose tolerance test, the usual liver function tests and the clinical course are according to Conn the four main points of the differential diagnosis of the various hypoglycemias.

That the possibility to diagnose a tumor of the I. of L. by clinical observation is not yet generally recognized, appears e. g. from a recent paper by Bertschinger (23), Switzerland. In his communication, which deals with two cases of spontaneous hypoglycemia, he writes i. a.: »... vielleicht handelt es sich um Hyperinsulinismus als Folge von Inseladenomen, die der klinischen Feststellung nicht zugänglich sind».

Gukelberger (24) very recently described a case of spontaneous hypoglycemia in which unfortunately the diagnosis was incomplete, the determination of the blood sugar value during an attack being omitted. Gukelberger is of opinion that an adenoma of the I. of L. is improbable as the Röntgenogram revealed no deviation in the duodenum bend, and as there were no pancreas pains nor other symptoms of pancreatitis. Adenomas of the I. of L., however, are not accompanied by pancreatitis symptoms, and a deviation of the normal course of the duodenum is only to be expected when the adenoma lies in the head of the pancreas and is at the same time very large. In our opinion in Gukelberger's patient the presence of a tumor of the I. of L. is not excluded. When in a patient suffering from hypoglycemia the attacks cease as soon as dextrose is administered, and when the liver, the hypophysis, the adrenal glands and the thyroid gland appear to function normally, hyperinsulinism becomes very probable. For discriminating between functional and organic hyperinsulinism the fasting blood sugar values should be determined and the dextrose tolerance test made. Fasting values below 50 mg % are a strong indication in favour of a tumor of the I. of L., and this diagnosis becomes even more probable when the syndrome shows a progressive character.

When organic hyperinsulinism is indicated, there is but one therapy: the operation. Our second case may serve as a striking illustration. In patients like this one a conservative therapy does more harm than good. The disease is progressive, and the regularly returning attacks of hypoglycemia are decidedly dangerous, for they may cause mors subita or permanent psychical aberrations, and it is not impossible that an originally benign adenoma may in the end lead to metastases!

As adenomas of the I. of L. are but seldom found in the head of the pancreas (of about 100 adenomas of which records were available to us, but 14 were localized here), we decided, when we operated for the second time, to a partial pancreatectomy. We hoped that the tumor would be present in the removed portion. Herein we were disappointed, but the third operation enabled us to rectify our mistake. The patient is still in possession of half his pancreas, but considering that there is some tendency to diabetes in his family (grandmother), it remains possible that the loss of part of his pancreas will do him harm in the future.

In accordance with our experience we fully agree with Whipple (11): »The writer would strongly emphasize the necessity of a very thorough search for tumor tissue before either the incision is closed or the decision to resect a large part of the pancreas — body and tail — is made and the resection is done. For the results after removal of islet adenomas are brilliant, whereas those after resecting the pancreas, especially if an adenoma is left in the remaining head, are very disappointing. The fact that in three of our own cases and in two others reported, an islet tumor in the posterior aspect of the head of the pancreas was not discovered until a second operation (in four) or at autopsy (in one) and partial pancreatectomy failed to relieve the hypoglycemic state, is strong evidence that the other failures, with removal of body and tail, were due to overlooked islet tumors. This emphasizes the importance of mobilization of the duodenum and palpation and inspection of the entire head of the pancreas before deciding on a partial pancreatectomy». Åkerberg (25) too shares this opinion. The transverse incision above the umbilicus according to Whipple is the best entrance.

The possibility that more than one adenoma may be present, must always be borne in mind. Whipple operated a patient suffering from spontaneous hypoglycemia, but only after a second operation, in which a second adenoma was removed, the patient was cured.

Moreover there are reports of adenomas revealed at autopsy, but overlooked during the operation [Ziskind (26), Friedman (27), Rienhoff and Lewis (28)]. As the adenoma has, as a rule, but a diameter of 1 to 2 cm, the examination during the operation should be very careful!

After the removal of the adenoma transient hyperglycemia sets

in (cf. fig. 5). This should not be forgotten, and at the right time a sufficient dose of insulin should be administered. The famous experiments of von Mering and Minkowski (29) (1889) with dogs in which after pancreatectomy diabetes set in, are instructive too in this connection. Nineteen out of the twenty test animals incurred a wound infection as soon as the hyperglycemia manifested itself. Therefore, as soon as hyperglycemia sets in, insulin should be given in order that the wound caused by the removal of the adenoma may heal under the most favourable conditions.

After the operation a regular control of the blood sugar values is necessary. In our patient we found that soon after the removal of the adenoma the blood sugar values began to rise. The same evening the patient received 15 U. insulin, and in the night the blood sugar concentration rose to 230 mg %. The next day the same dose was administered three times, after which the blood sugar values became once more normal. Four weeks after the operation the oral curve was nearly normal; three months and also eight months later the oral curve was once more determined, and proved to be entirely normal. This passing form of diabetes has been described by others also. Values up to 400 mg % have been reported [Windfeld (12)]. How is this hyperglycemia to be explained? After the removal of an adenoma of the parathyroid gland a passing tetany may show itself, and this has taught the surgeon the necessity of administering to the patient for some days after the operation calcium and parathormone; this treatment to be continued untill the equilibrium is restored. The removal of an adenoma of the I. of L. will probably cause a similar disturbance.

The constantly low blood sugar values suggest a high concentration of insulin in the blood. It is therefore quite possible that the concentration of the contra-insular hormones produced by the hypophysis, the adrenal glands and the thyroid is also higher than normal. The abrupt cessation of the insulin production might cause a passing dominance of these contra-insular hormones and consequently a temporary hyperglycemia, this condition maintaining itself untill the equilibrium is restored.

In hypoglycemias of the organic type, e. g. in our second patient, the attacks as a rule occur after fasting; usually therefore in the morning. One of Windfeld's patients at first had them on Sundays only; on these days he rose later than usually, and breakfasted at a

later hour. In the psychiatric department the syndrome was recognized as insulin shock.

The part played by the liver in the origin of the attacks should also be shortly discussed. The endogenous liver rhythm of Forsgren (30), which consists of an assimilatory and a dissimilatory phase, might in the assimilatory phase, i. e. in the phase in which the synthesis of glycogen from dextrose of the blood takes place, and which occurs in the early morning, favour the outbreak of a hypoglycemic attack. Åkerberg (25) moreover is of opinion that »A low blood sugar level does not cause a compensatory glycogenolysis during that part of the day when the liver is working assimilatively». Biopsy of the liver [method Iversen-Roholm (31)] of a patient suffering from dyspepsia (the disease, however, is in this connection without importance), respectively at 8.45 and at 16. —, revealed no difference (the liver parenchyma was fixed in 96 % alcohol and subjected to Best's glycogen staining method). In a second patient too the biopsy did not reveal a clear difference; this time the samples were taken respectively at 11.30 and at 23.30. For the time being we are therefore inclined to agree with those authors according to whom the importance of the liver rhythm for the origin of attacks of hypoglycemia is as yet unproved.

Windfeld (12), and others also, regard a rapid decrease of the blood sugar value as an important factor in the origin of an attack. In view of the form of the curves obtained from our second patient when sugar was intravenously injected, it seems to us that this is not always so.

The success of the third operation leads to the conclusion that the small adenoma was indeed the cause of the attacks of hypoglycemia. It is quite possible that the tumor produced a superabundant amount of insulin. The amount of insulin in a normal pancreas is 2—3.5 U. per gram tissue. From an adenoma too insulin can be extracted. Howland (4) et al. were the first to report on this; the determination itself was carried out by Best, and was qualitative only (1929). Åkerberg (25) found in the adenoma of his patient 8 U. per gram tissue; Windfeld (12) found in one adenoma 15 U. and in another 20 U.; and Munakata (17) reported 27.7 U. Best (32) recently, in a survey, mentioned an amount as high as 85 U. per gram tissue. In the adenoma of our second patient somewhat more than 5. U. per gram were found (Overbeck). This adenoma weighed

slightly more than 1 g and contained therefore more than 5 U. insulin. A normal pancreas of about 100 g comprises about 10 g islet tissue, and contains 200 to 350 U. insulin; the amount of insulin found in our adenoma (about 5 U.) is therefore too low to explain the syndrome. It should not be forgotten, however, that our method of investigation is not perfected to the same degree as in America. According to Hagedorn (33) the insulin concentration of the adenoma is the same as that of healthy islet tissue, but this is in

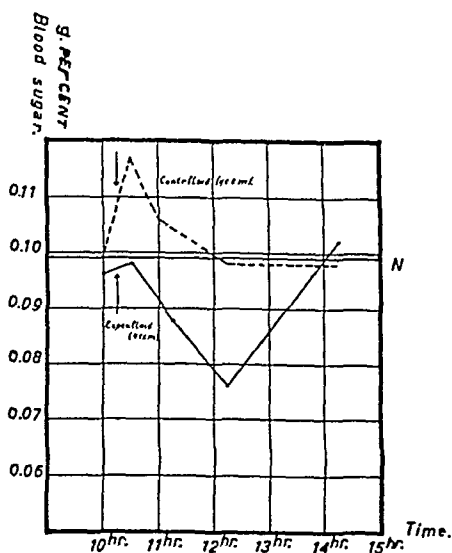


Fig. 9. ----- blood sugar curve after injection of control culture fluid.
 ————— blood sugar curve after injection of the tissue culture fluid.

disagreement with Best (32). Possibly the adenoma produces insulin continuously [Åkerberg (25)]. A satisfactory explanation, however, is not yet possible.

Tissue cultures of adenomas have also been attempted. Margaret Murray (34) in 1935 started tissue cultures from two adenomas; her intention was to use them in diabetes treatment. After four weeks one of the tissue cultures was transplanted in the axilla of a female diabetic patient, but a result was not obtained. One of the adenomas removed by Windfeld (12) was used by Fischer for tissue culture. Hagedorn (33) examined this culture in order to find out whether insulin was present, but neither in the tissue itself, nor in the substrate it could be found [cf. Windfeld (12)].

Dr Gaillard (from the Department of Histology of the State University, Leyden) was kind enough to carry this through. Al-

though at first inclined to assume that the cultivated tissue indeed produced insulin, we afterwards became sceptical with regard to these results, the effect on the blood sugar value of the test rats not being sufficiently clear. Since then however, we could supply Dr Gaillard with an adenoma obtained from a patient of Dr Lups, Utrecht, Holland. We wish to thank Dr Lups for his benevolence in transmitting to us this adenoma. This time Dr Gaillard succeeded in obtaining with his culture fluid a decrease in the blood sugar level of the test rats (fig. 9).

Conclusions:

I. The syndrome of hypoglycemia, a condition that may be regarded as dangerous, shows a great diversity of aspect, and is still too little acknowledged.

II The cause of spontaneous hypoglycemia is sometimes of an organic, and sometimes of a functional nature.

III. As the treatment will have to depend, as much as possible, on the underlying cause, a detailed differential diagnosis is imperative.

IV. If the hyperinsulinism proves to be of an organic nature, the only admissible therapy is operation! A transverse, slightly bent incision above the umbilicus according to Whipple is recommended for the opening of the abdomen.

V. Carcinoma of the I. of L. seems to be rare. Only seven cases have been reported; ours being the eighth. Metastatic nodules are found mainly in the liver, but sometimes also in the parapancreatic lymph glands. From these metastases a substance can be extracted that in rabbits causes a decrease of the blood sugar concentration.

VI. Adenomas of the I. of L. are less rare than until recently was assumed. They may show signs of malignancy, and finally form metastases. The operation therefore should not be indefinitely postponed.

VII. If the adenoma is not seen or palpated either in the tail or in the body of the pancreas, the duodenum should be mobilized in order that the head may be inspected and palpated, before deciding on a partial pancreatectomy.

VIII. After the removal of the adenoma a transient hyperglycemia sets in. During this time insulin should be administered in order to prevent infection of the wound.

IX. The possibility is discussed that contra-insular hormones may play a part in the pathogenesis of this postoperative hyperglycemia.

X. If microscopically tumor cells are noticed in the venules of the adenoma, the existence of metastasis towards the liver is not necessarily involved. As the adenomas are strongly vascularized, it is quite possible that the tumor cells may have passed into the bloodvessels during the enucleation.

XI. The history of a successfully operated patient is used for a detailed discussion of the diagnosis, the treatment and the pathology of the disease. A close cooperation between clinician, surgeon and pathologist leads in such cases to more satisfactory results than could otherwise be expected.

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From the Medical Clinic of the University, Upsala, Sweden. (Chief: Prof. G. BERGMARK.)

Seasonal variations in the occurrence of pernicious anemia.

By

SIGURD WENDT.

(Submitted for publication August 7, 1942).

It has long been known that a number of diseases, also non-infectious ones, have a predilection for certain seasons. As examples might only be mentioned peptic ulcer and hypochromic anemia. The cause of such a seasonal variation is probably to be sought in a connection between external factors conditioned by the seasons and their effect on the organism's resistance, which last varies with the different times of the year.

It has been shown earlier, by Saltzman (1), that the occurrence of pernicious anemia, too, undergoes seasonal variation. His material consists of 194 cases of idiopathic and 326 cases of bothrioccephalus pernicious anemia, treated at three Helsingfors hospitals during the years 1883—1913. The account showed that these closely related diseases, taken together, displayed a seasonal variation in their appearance in that 343 — or $\frac{2}{3}$ — of the individuals applied for hospital treatment during the months March—August, while one third was spread over the remaining six months.

A similar tendency can be seen in a paper by Strandell (2). Here the material consists of 117 cases, treated at Serafimerlasarettet during the time 1913—1930.

A scrutiny of the available haematological literature, however, seems to show that the question of this kind of seasonal variation has not otherwise been the subject of observation.

An increased knowledge of the nature of the disease and improved methods of diagnosis have, during recent years, made possible a more reliable diagnosis. It has been possible to distinguish severe anemias of other kinds than the pernicious, and also to classify less pronounced cases of pernicious anemia under their correct heading; in brief, a greater uniformity has been attained as regards the diagnosis.

On these grounds, Doctor J. Waldenström has urged me to review the cases of idiopathic pernicious anemia treated during the last 12 years at the Medical Clinic in Upsala, with special reference as to whether there really is a statistically significant seasonal variation in the occurrence of the disease.

This investigation has both confirmed such a seasonal variation for admittance to hospital, and also shown that the time the patients fell ill seems to be conditioned by the season of the year.

The material consists of all the cases of pernicious anemia (p. a.), that were treated at the Medical Clinic during the years 1930—1941, that were resident in the province of Upsala (Upsala län) at the time of admittance; none of them had received liver treatment previously. During the period mentioned, practically all the recognized p. a. cases of the district received their diagnosis and therapy at this clinic; a small number of questionable cases from the first two years have been left out of account. The diagnosis is ensured by the effect of *only liver therapy* (peroral treatment up to 1931 inclusive and since 1932 injection therapy) with counting of reticulocytes and control until normal blood values were reached, and, as a rule, also by *gastric analysis* (since 1931 fractionated testmeal, with histamine), *X-ray examination of the stomach*, and since 1934, by *sternal puncture*. In practically all cases from 1939 inclusive the *value for serum iron* has also been determined [according to the method of Heilmeyer and Plötner modified by Vahlquist (3)] generally both before and during the therapy [see Waldenström (4)]. Thus, for the first two years the diagnosis can be taken as practically uniform, and for the time 1932—41 as absolutely certain.

The material comprises 190 cases, 59 men and 131 women, or, in per cent, 31.1 % and 68.9 % respectively. The percentage of males in the whole of the district's population at this time was 49.2. Were both sexes liable to the same risk of falling ill with

p. a., the men might have been expected to have done so to $49.2\% \pm$ the material's standard error. This is calculated according to the formula $\varepsilon(p) = \sqrt{\frac{p \times (100-p)}{n}}$, where p gives the percentage

and n the number of observations — i. e. $\varepsilon = \sqrt{\frac{49.2 \times (100-49.2)}{190}} =$

3.6 %. The expected percentage is thus 49.2 ± 3.6 . The percentage observed for the male patients falls outside these limits, however, and also outside the limits marked by $49.2 \pm 3 \times \varepsilon$. There is thus a preponderance of female patients, provided, of course, that p. a. was diagnosed to an equal degree in the two sexes. As my material comprises practically all cases of p. a. in the district there is certainly a real preponderance of women. This tallies well with earlier reports on this subject from Germany and Scandinavia. The situation in England, however, differs in an interesting way from these above mentioned. According to Wilkinson (5) there were among 700 cases 52 % women and 48 % men, thus no significant difference. In the United States the relation between the sexes seems to differ even still more from ours in that men are said to be slightly more commonly affected than women [Castle and Minot (6)].

At the time of admittance to hospital, 59 cases, or 31.1 % were living in either of the two towns (Upsala and Enköping). The proportion of the town-dwellers in the district's entire population was during the 12-year period in question 29 %. It could therefore be expected that, of the 190 cases, $29\% \pm$ the standard error $\sqrt{\frac{29 \times (100-29)}{190}}$ or $29 \pm 3.3\%$ would be town-dwellers.

The observed value of 31.1 % lies very well within these limits. The material thus shows a good accordance between the risk of falling ill with p. a. in the towns and in the countryside.

It may perhaps seem strange to compare Upsala and Enköping with the major industrial towns of England. In these latter, however, a decidedly higher frequency for p. a. has been observed than in the rest of the country [Wilkinson (5)]. This is almost certainly due to the fact that better diagnoses are obtained in towns than in the country. Social conditions, such as wealth or poverty, luxury or filth, occupation, over-exertion or the like, do not seem to have exerted any influence [Wintrobe (7)].

The patients applied for hospital treatment in general about 6 months after the subjective symptoms had begun to make themselves felt. The number of years that had elapsed previous to their falling ill can therefore be regarded to be practically the same as their age on admittance to hospital. The age distribution can be seen from table 1 below.

Table 1.

Age group.	Number of all individuals in respective age groups.	Percentage of total population.	Number of p. a. cases in each age group.	Percentage of total cases with p. a.	Number of p. a. cases on 10.000 of the general population in each age group.
30—39	20963	14.1	13	6.8	6.2
40—49	17867	12.8	18	9.5	10.1
50—59	14028	10.0	50	26.3	35.6
60—69	10283	7.3	65	34.2	63.2
70—79	7009	5.0	43	22.6	61.3
80—89	2154	1.5	1	0.5	4.6

The youngest patient fell ill at 34 years of age and the oldest at 83; most of the others between the ages of 50—75. The mean age was 60.8 years.

Data which the literature provides on this point generally show patients to have fallen ill some ten years earlier.

The number of p. a. cases diagnosed yearly made 0.6 % of the total number treated at the Clinic and 0.114 ‰ of the whole population of the district. Waldenström (8) has recently shown that there are about 150 persons with diagnosed p. a. in the district at present; this means that more than 1 in every 1000 has this disease. A further increase can be expected during the next few years, on the same grounds as, for example, the increase of diabetics after the introduction of the insulin therapy.

The clinical records have further been studied to elicit from the anamneses the probable time of the year when the patient fell ill — i. e. the time he or she first reported feeling a symptom which might be caused by p. a. When the initial falling ill seems to have been followed by a remission and then by a fresh relapse, the first attack is taken as marking the start of the disease. It is in the nature of the thing that the anamnestic data have not

always been as reliable as might be wished. Not only is it often hard for a patient to give the date when an insidious symptom really started, but also the patients do not all have the same power of observation and memory; then, too, the quality of the records vary with their writers, who have sometimes not always been sufficiently aware of the importance of exact data as to time. All this has made it necessary to exclude 23 cases where the time of falling ill was too vaguely given. In the remaining 167 cases, the information has for natural reasons varied a great deal as regards placing the first appearance of the symptoms. Some patients have

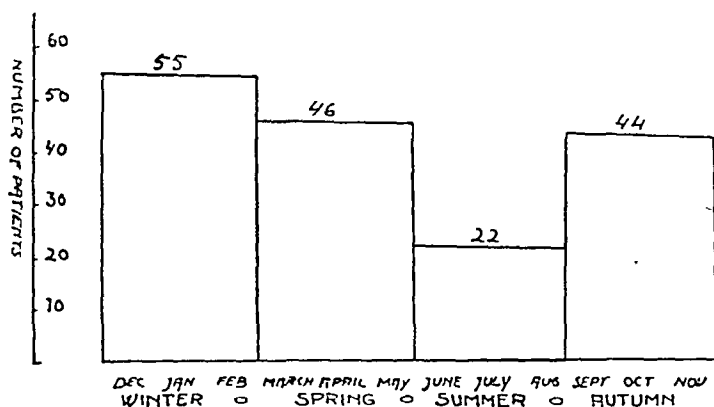


Fig. 1. Diagram showing the seasonal distribution of the onset of the disease.

given this time within a month or even more exactly; others, again, have given reports as »the last half year», »last winter», and the like. It has therefore been found suitable to group the cases into three-month periods (June—August, September—November, and so on) which, roughly speaking, correspond to our idea of the seasons.

The diagrams below show the seasonal distribution of the onset of the disease (fig. 1), and in fig. 2, the number of patients admitted per month (broken line) and per season (unbroken line).

For the following statistical treatment, the time both of falling ill and of admittance to hospital is tabulated below in season groups.

As the table 2 shows, the figures display a seasonal variation. Taking into account the relatively modest extent of the material, this variation might possibly be ascribed wholly to chance. To discover whether this is so or whether other factors — such as are conditioned by the seasons — play a part, the figures must be submitted to a statistical treatment.

If the disease were not conditioned by changes of season, a large material would show 25 % of its cases in each three-month period. In the grouping according to the season when the disease set in, where the material consists of 167 cases, the highest per-

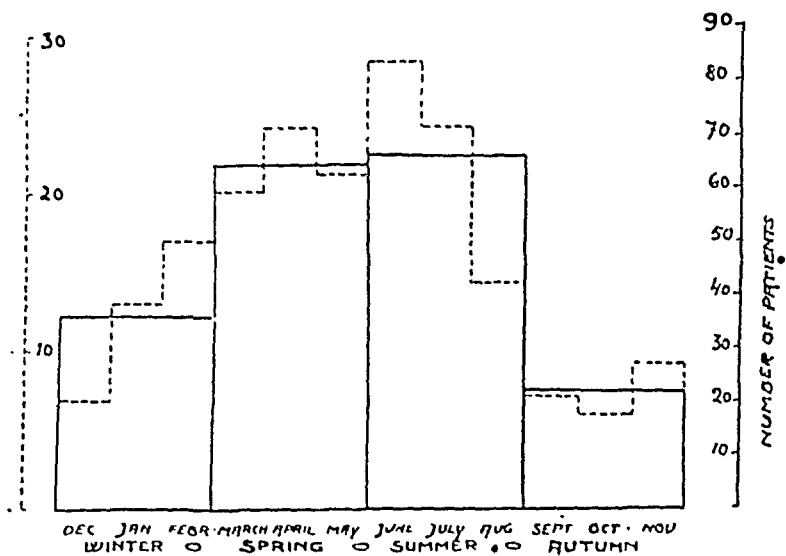


Fig. 2. Diagram showing the time of admittance to hospital.

Broken line: number admitted per month.

Unbroken line: number admitted per season.

Table 2.

Season	Fell ill		Admitted to hospital	
	number	%	number	%
Winter (Dec.—Feb.)	55	33.0	37	19.5
Spring (March—May)	46	27.5	65	34.2
Summer (June—Aug.)	22	13.2	66	34.7
Autumn (Sept.—Nov.)	44	26.3	22	11.6
Total	167	100.0	190	100.0

centage is found for the period Dec.—Feb., namely 33 %, and the lowest for the period June—Aug., namely 13.2 %. The stan-

dard error obtained for this material is $\sqrt{\frac{25 \times (100-25)}{167}} = \pm 3.35$

(the same formula as was given above). If we look first at the 13.2 % of the summer period, we find that this figure is under 25 % by more than 3 times the standard error — i. e. the decrease in the frequency for the period in question is statistically signifi-

cant and not just due to chance. The value for the winter period, 33 %, does not deviate so much, yet all the same it exceeds 25 % by 2.4 times the standard error; this shows that the increase for this season is statistically highly probable if not absolutely significant. A larger material would very likely have yielded statistically significant figures on this point.

The distribution of the admittance similarly shows a seasonal variation, see table 2. Here, as has been mentioned before, it was possible to include all the 190 cases. Applying the same statistical method as above, a standard error of $\sqrt{\frac{25 \times (100-25)}{190}} = \pm 3.14$ is obtained. A statistically significant frequency increase can thus be observed in percentages of more than $(25 + 3 \times 3.14) = 34.4$ %. The percentage figure of the summer period exceeds this, that of the spring period practically reaches this level, exactly calculated to $25 \% + 2.9$ times the standard error, so that it is possible to establish a significant increase in the admittance frequency for the summer period, and a practically significant one for the spring. The 11.6 % of the autumn period is far below $25 - 3 \times 3.14 = 15.6$ %, which indicates that this time shows an unquestionably diminished admittance frequency.

Discussion.

The seasonal distribution of the time the patients fell ill is based on their own anamnestic informations. As has been said above, the reliability of these last vary; nevertheless there are probably no real grounds for suspecting their exactness to show a systematic error to vary according to any one system, e. g. that the patients would, with a certain consistency, remember wrongly. There is therefore reason to believe that the subjective onset really shows a seasonal variation.

Objections can be made to the seasonal distribution advanced for the time of admittance, such as that a sick but not totally invalid person waits for a shorter or longer period before applying for hospital treatment until working conditions and other environmental factors permit of his doing so. This is certainly to some extent the case as regards p. a. also, but if the seasonal variation were wholly or for the most part due to such circumstances, it

would hardly be likely to find the highest frequency during spring and summer — the busiest time for an agricultural population from which more than $\frac{2}{3}$ of the cases in this material came. The total number of patients admitted to the Clinic during the same space of time shows relatively small seasonal variations, which are not statistically significant; any tendency they show would be rather a diminished admittance in the summer, while the number of p. a. patients admitted shows at the same time a statistically significant increase. See table 3.

Table 3.

Pernicious anemia patients compared with the total number admitted during the period 1930—1941.

Season	Total admittance		P. a. patients	
	Number	%	Number	%
Winter (Dec.—Feb.)	8085	25.5	37	19.5
Spring (March-May)	8362	26.5	65	34.2
Summer (June-Aug.)	7244	23.0	66	34.7
Autumn (Sept.-Nov.)	7911	25.0	22	11.6
Total	31602	100.0	190	100.0

The seasonal distribution of p. a. is probably, on the above grounds, linked up with one or more of the factors which make the disease what it is. In other words, there is something of importance for its etiology which has a predilection for a certain part of the year. A thought readily presenting itself is that this is due to a seasonal, i. e. an exogenous factor, conditioned by an injurious agent or perhaps, rather, by a deficiency of some factor necessary for erythropoiesis.

A striking fact is that the subjective symptoms do not reach such a degree as to prompt visiting hospital until the spring and summer. Sufferers from ordinary hypochromic anemia, on the other hand, often are most troubled during the cold seasons; they feel cold and generally unwell and if they seek a cure, they might be expected to do so for the most part during winter and spring, when it is still chilly. The fact that such a large proportion of the p. a. patients do not apply for treatment until the spring and summer must be taken to mean that some essential element of the disease has the tendency to set in during these seasons.

The knowledge of and interest in p. a. is different in different quarters; this doubtless means that attention is paid to the disease to a varying degree. Data as to its occurrence should therefore be taken with certain reservations. In earlier times, it was maintained to be rare in the black race. Yet it does not seem to be so strikingly unusual among the negroes in America; a non-selected material from the Johns Hopkins Hospital, where about as many negroes as whites are treated, showed for a period of 2 years 10 negroes and 54 white people with this complaint [Wintrobe (7)]. It seems allowable to state, however, that different races are affected to different degrees. Thus, for example, the disease is said practically never to be found in Japan [Katsunuma (9) and others] or China [Keefer and Yang (10)], while it is common in Northern Europe. Further, a variation in the geographical distribution has been found, probably to some extent connected with this racial dissimilarity. The complaint is thus reported as being most usual in the temperate zones [Wintrobe (7)], and unusual in the tropics [Schilling (9)].

The question then arises whether the increased onset in the winter which is observed here, and the relatively rarity of the disease in the tropics, may not possibly be linked up with meteorological factors and the conditions of living these set up.

Manifest p. a. is probably often preceded by a lengthy pre-anemic condition. It is known, for example, that gastric analyses have often shown achylia many years before the clinical onset of the complaint. It is reckoned that this sign of insufficiency in the function of the stomach is sooner or later followed by another, namely a successive diminution in the production of the intrinsic factor, and that erythropoiesis will be upset when the amount of this factor is inadequate. It is therefore no doubt unwarrantable to ascribe any more primary etiological significance to the above-mentioned seasonal factor. On the other hand, it is conceivable that this factor has a releasing rôle in the development of the disease, either by further inhibition of the already falling production of the intrinsic factor, or else by establishing an insufficiency in the food as regards the extrinsic or anti-p. a. factor.

Summary.

Practically all the cases of true pernicious anemia diagnosed in the district of Upsala (Upsala län) during the years 1930—1941 have been submitted to classification and statistical treatment.

In so doing, it has been found

1) that the frequency of the disease was greater for women than for men, in the ratio of about 2: 1,

2) that there was no difference between the frequency in the towns and in the country,

3) that the greatest frequency was found among 60-years-olds,

4) that the time of getting the first symptoms varied with the seasons, so that it seems to have been greatest during the winter and has been found to have been least during the summer,

5) and that also, and even more distinctly, the admittance frequency showed a seasonal variation, so that probably the spring and certainly the summer displayed an increased frequency, and the autumn a lowered one.

Possible sources of error for the two last observations have been considered. The seasonal occurrence of pernicious anemia has been linked up with a supposed seasonal factor, which is assumed to be the releasing factor in the manifestation of pernicious anemia.

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(From the Biochemical Institute of the Copenhagen University (Chief: Professor R. Ege, Ph. D.) and the Rigshospital Dept. of Pediatrics (Chief: Professor C. E. Bloch, M. D.)

Investigations into the Cause of the Physiological Hypoprothrombinemia in New-born Children.¹

III. The Vitamin K Content of Feces of Infants and Adults.

By

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(Submitted for publication May 2nd, 1942).

The view has been held that the formation of vitamin K by intestinal bacteria must play a dominating role in the supply of this vitamin to the individual, whether new-born or adult.

Almquist & Stokstad (1) have shown that foodstuffs in a state of putrefaction contain vitamin K, and they have studied the ability of certain bacteria to form this vitamin. Of the ordinary intestinal bacteria most vitamin K is formed by *Coli*, about 1000 Dam and Glavind units per gram of dry substance, whereas only very small quantities are formed by the lactic acid forming group. (7)

The intestinal tract of new-born children is practically sterile; intestinal flora develops during the first 1—3 days after birth, the number of *Coli* bacteria in breast-fed children increasing more slowly than that of the other intestinal bacteria (*Streptococci*, *B. acidophilus*, *B. bifidum*). As the prothrombin content of the blood of new-born children is found to be lowered in the first days of life, the cause was thought to be a lack of vitamin K-forming

¹ With the support of King Christian X's Jubilee Fund and the Rockefeller Foundation.

bacteria in the intestine. In individuals with a normal intestinal function, which presumably means normal intestinal flora, a lack of vitamin K is practically never seen; the literature contains only one reference to alimentary K-avitaminosis in adults, demonstrated by a special method. (4)

It is not known where in the intestinal tract the absorption of vitamin K takes place; but as it is known that the absorption depends on the presence of bile acids, the assumption is reasonable that the absorption takes place chiefly in the small intestine. Therefore it would be of interest to examine the intestinal flora and the vitamin K content in the various sections of the intestines. Investigations of this kind are almost impossible to undertake on man, and consequently we have merely examined the vitamin K content in the feces of normal adults, of pregnant women, and of children of various ages. The literature contains only one investigation into the vitamin K content of feces, by Dam (2), who in feces lipid found 2000 D & G units per gram.

Method.

The vitamin K content is determined in a petrol ether extract of feces, prepared in the following manner: A weighed portion of fresh feces (10 to 20 grams), or feces stored in a refrigerator at about -2° , is stirred in a mortar together with anhydrous sodium sulphate. After being allowed to stand a while the mixture is stirred three times with ample petrol ether, which is filtered off through a Jena glass filter, 3G3. The filtrate is poured into a previously weighed 50 cm³ normal ground-joint-flask, joined by a stop-cock with a suction pump, and dried by evaporation at $40-50^{\circ}$ C. The flask is then weighed again. The weight difference gives the lipid content in feces. At the same time a smaller portion of feces, about 1 gram, is weighed in a small glass dish and dried at 100° C to constant weight for determining the dry substance in feces. In this manner the vitamin K content is determined in proportion to the weight of fresh feces, dry substance and feces lipid.

The lipid is now made into tablets, a weighed quantity of tablet mass, consisting e. g. of a mixture of lactose, talcum and salep, being transferred to the flask containing the lipid. Lipid and tablet mass are then mixed thoroughly in the flask by stirring with a nickel

spatula after adding a little petrol ether (if necessary) in order to remove all the fat from the walls of the flask. The entire process is undertaken in a very faint light and the tablets are stored in darkness in the refrigerator.

The Determination of Vitamin K.

The vitamin K content is determined by Dam & Glavind's curative method. (3) The principle of this method is that the substance to be assayed for vitamin K is administered for three successive days in the form of tablets to K-avitaminotic chicks. The prothrombin content of the blood is determined before and after the tablets are administered. When determining the prothrombin the so-called R-value is found. $1/R$ is a measure of the prothrombin content of the blood in relation to the normal. The vitamin K content in the tablets is calculated from the increase of $1/R$; for this purpose a curve is used, based on experiments with a standard substance and showing the increase of $1/R$ in relation to the quantity of standard substance administered. The results are shown in units, 1 Dam & Glavind unit being defined as the quantity of vitamin K contained in 2 mg of the dried spinach employed as the standard. 1 mg of the vitamin K, K_2 , formed by the activity of the intestinal bacteria, has 8000 units, whereas the K_1 in green plants has 12,000 units per mg.

Determinations of Vitamin K in the Feces of Normal Adults.

The vitamin K content was determined in the feces of some normal adults. The individuals were kept for three days on a diet that is relatively deficient in vitamin K, containing no greens or liver. Care was also taken that the diet contained only moderate quantities of fat in order that fluctuations in the lipid content should not have too great an influence on the absorption of vitamin K or on the quantity of lipid per gram dried feces.

One adult (P. P.) was observed for some days. The results are given in Table 1. This table, like those following, shows the percentage of dry substance in feces, the percentage of lipid in the dry substance, and the vitamin K content, in units per gram, in feces lipids and feces dry substance. The tables also show the number of chicks

Table 1.

Vitamin K content in feces. Feces from five different motions from a normal, adult male (P. P.).

Date	Dry substance per cent	Lipid per cent	Vitamin K units per gram		Number of chicks
			lipid	dry substance	
Sept. 11	24.1	5.6	2000	110	3
» 12	17.6	6.2	1000	60	3
» 13	22.6	6.3	1100	70	2
» 15	17.1	6.8	2500	170	3
» 15	20.6	6.3	3000	190	3

Table 2 shows the vitamin K content in the feces of five normal adults.

Table 2.

Vitamin K content in feces of five normal adults.

Name	Sex	Dry substance per cent	Lipid per cent	Vitamin K units per gram		Number of chicks
				lipid	dry substance	
E. L.	M	19.3	10.0	1100	110	3
A. L.	F	15.4	11.7	2000	230	3
G. G.	F	30.7	4.8	3000	140	3
J. G.	M	13.6	9.7	2000	190	2
P. P. (see Tab. 1)	M	17.1—24.2	5.6—6.8	1000—3000	60—190	—

employed in the determination; varying quantities were given to the different fowls. A correspondingly greater accuracy will be obtained when a large number of chicks is used.

The results suggest that there are no great variations from day to day in the same individual, or from one individual to another. No difference was observed between males and females.

Assuming a daily quantity of feces of about 200 grams this means that from 4000 to 8000 units of vitamin K are excreted with feces daily. The daily quantity of bacteria excreted in feces is given by Kendall (5) at about 3×10^{12} ; if all the bacteria were *Coli*, the total weight would be about 60 grams and their vitamin K content would be about 12,000 units. Accordingly, there are reasons for assuming that the vitamin K demonstrated in feces result from the intestinal bacteria.

Table 3.
Vitamin K content in feces of six pregnant, normal women.

Case Record No.	Age years	Month of pregnancy	Dry substance per cent	Lipid per cent	mg per gram per day	$1/R_1$	$1/R_2$	Prothrombin time in seconds
237L/41	26	9	13.9	13.4	3.45	0.02	0.24	15.2
251L/41	18	9	12.0	7.4	5.14	0.01	0.41	16.3
261L/41	18	8	33.0	6.1	7.95	0.01	0.90	16.5
263L/41	37	8	38.0	8.5	8.5	0.01	1.28	15.8
250L/41	40	8	23.0	5.8	6.0	0.01	0.41	17.0
262L/41	20	9	33.0	5.1	5.3	0.01	1.28	17.2

Determination of Vitamin K in Feces of Normal, Pregnant Women.

As the prothrombin content in the blood of pregnant women is increased, often considerably, and regarding the possibility that an increased quantity of vitamin K in the contents of the intestine might be the cause of the higher prothrombin level, we judged it to be of interest to ascertain the vitamin K content in feces of pregnant women. An examination was made of the feces of six individuals; tablets were prepared from each portion of feces, and their effect on the prothrombin of K-avitaminotic chicks was tested. Only one chick was employed for each sample of feces, so that no exact standardization was carried out. The results are shown in Table 3. Thus this table does not give the number of units per gram, but instead the quantity of lipid administered daily per gram of chick weight (mg per gram per day), as well as the prothrombin values for the chicks prior to and after investigation ($1/R_1$ and $1/R_2$). The table also includes the prothrombin time of the women, measured by a modified form (9) of Quick's method (10); the normal value determined at the same time was 20.5 seconds.

As was stated, the figures do not permit of an exact calculation of the vitamin K content. However, the conclusion may be drawn that three women, 237, 251 and 250, if anything are a little below the normal material, whereas the other three may be higher. As the prothrombin value was the same for these two groups of pregnant

women, these tests have not provided evidence of any relation between the vitamin K content in feces and the prothrombin content of the blood.

Determination of Vitamin K in Feces of New-born Children.

It is known that meconium contains practically no bacteria. It is not until the third or fourth day of life that excretion of real feces is beginning, and bacteriological studies have shown that at this stage the number of bacteria rises abruptly to quantities of the same order as those found in older children and adults. In the majority of normal children the prothrombin in the blood falls conspicuously in the first three or four days of life, whereafter it rises, first quickly and then slowly to the value found in adults. Accordingly it is of interest to examine the content of vitamin K in the feces of children in their first weeks of life. As it is known that the intestinal flora of breast-fed children and artificially fed children differs to a marked degree, the intestinal bacteria of the former consisting mainly of the lactic-acid-forming bacteria *B. acidophilus* and *B. bifidum*, whereas in the latter they are chiefly *Coli* bacteria, the feces of children of both categories have been examined. The individuals were four children exclusively breast-fed, three solely artificially fed, and one child at first breast-fed and afterwards artificially fed. The artificial diet consisted of one part cow's milk and two parts of 2 per cent barley water with 4 per cent sugar, 20 to 30 grams five to seven times per day. We made tests to ascertain whether the vitamin K content rose when feces were stored for about 8 hours at about 20°, but found no change in the values of either category. Nevertheless the napkins were examined more frequently than usual and any feces were removed immediately and stored in a sterile tube at 0°C until extraction as above described could be made. In order to obtain a quantity of feces suitable for standardization, all feces for a certain period, which is shown in Table 5, were put together and extracted simultaneously.

In respect of one artificially fed child we endeavoured to determine the vitamin K content in each stool. Owing to the small quantities of feces the entire extract from each stool was employed for one chick only, so that there was no actual standardization in

Table 4.

Determination of vitamin K in feces from an artificially fed, new-born child (born Dec. 6 at 6.40 p.m. Case record No. 1845B/40). Prothrombin determined by Plum & Dam's method (Normal Value 25 Sec.) *

Date	Hour	Dry substance per cent	Lipid per cent	Vitamin K units per gram		Prothrombin time	
				lipid	dry substance	date	sec.
Dec. 9.	17.30	13	53	2000	1000		
» 11.	7.15	29	13.3	500	60	Dec. 7.	70
» 11.	13	24	7.6	1500	140	» 10.	56
» 13.	7.30	31	7.5	<1000	<100	» 12.	39
» 13.	10	24	7.0	2000	300	» 16.	40
» 15.	7.15	40	14.3	1000	150	» 19.	36
» 15.	17.15	27	33.4	1000	300		
» 16.	3.30	26	9.0	<1000	<100		
» 16.	15	40	10.6	1000	100		
» 17.	7.20	29	18.5	>5000	>1000		
» 17.	17.15	20	2.0	>1000	>25		
» 18.	23.15	22	2.9	10000	300		
» 19.	7.10	27	3.3	<5000	<150		
» 19.	17.30	23	9.9	1500	150		
» 20.	7.30	20	5.0	2000	100		

this case. Nevertheless, we have expressed the results in units for purposes of comparison. The figures indicate merely the approximate quantity of vitamin K content; where the content was very low it was possible to give merely a maximum value, and where it was particularly high, so that a normal prothrombin level was obtained, the table shows the minimum value (Table 4).

Although only one chick was employed for each test, and the figures consequently are only approximately correct as already stated, the table gives the impression that there must have been markedly great variations of the vitamin K content in the various samples of feces, even when they are from the same day. Another striking feature is the great fluctuation of the percentage of lipid extracted with petrol ether. Apparently there is no correlation between the fluctuations in the vitamin K content and the lipid content.

Considerable quantities of vitamin K were found in the very first sample of feces, when the child was three days old. As the quantity of vitamin K of the artificial diet would scarcely exceed

Table 5.

Determinations of vitamin K in feces from 7 normal new-born children. Prothrombin determined by Plum & Dam's method (Normal Value 25 Sec.)

Case record no.	Diet	Age days	Dry substance per cent	Lipid per cent	Vitamin K units per gram		Number of chicks	Prothrombin time	
					lipid	dry substance		Age in days	Time in seconds
603B/41	Breast	1	22	5.7	< 100	< 5	1	1	49
»	»	2	26.5	11.9	< 100	< 10	2	3	97
»	»	3—9	23.4	13.3	< 100	< 10	2	5	146
								7	107
651B/41	Breast	3—8	26.5	20.6	< 50	< 10	2	1	69
								3	74
								5	61
								7	56
687B/41	Breast	1—7	34.6	24.2	< 150	< 10	2	1	106
								4	321
								8	77
780B/41	Breast	0—12	24.0	25.8	< 150	< 10	1	1	32 ¹
								4	30
								8	35
1340A/41	Artif. (milk mix.)	1—2	24.2	29.0	ca. 100	ca. 30	1		
		3—4	25.4	27.1	100	30	2		
		5—6	21.5	13.5	400	50	2		
		7—8	21.0	22.4	170	40	2		
		8—10	23.4	16.9	60	10	2		
1347A/41	Artif. (milk mix.)	0—2	18.4	3.0	100	3	3		
		2—7	17.8	22.6	60	15	2		1
		9—11	20.5	13.1	110	15	2		
369B/41	Breast	0—1	45.3	5.9	< 500	< 20	2	1	69
	»	2—3	34.5	16.6	< 500	< 50	1	3	245
	»	4—7	24.2	37.7	< 200	< 100	2	4	191
	Artif. (milk mix.)	8—13	25.0	22.5	< 200	< 50	2	6	52
		13—16	21.7	23.8	50	10	4	8	53
		17—21	22.6	9.3	400	35	2	10	46
		21—25	23.6	9.8	< 500	< 50	1	13	44

¹ Prior to delivery the mother received 10 mg 2-methyl-1,4-naphthohydroquinone sodium disulphate perorally.

100 units a day, the excreted quantity must have been formed in the intestinal tract.

For the purpose of securing feces enough for standardization we then proceeded to examine larger quantities, obtained by putting several successive portions together (Table 5).

In every case where real standardizations were made of the vitamin K content in the feces of new-born children, the content is of a value that is much less than that in the feces of normal adults.

Up to the 8th—12th day the vitamin K content in the feces of the three breast-fed children was so low that it could not be determined by the method employed.

On the other hand, in the feces of two of the artificially fed children there were already demonstrable quantities of vitamin K in the united portions collected from the first three days of life; and in the samples from the artificially fed child in Table 5 there were considerable quantities of vitamin K in the portion first examined, taken on the fourth day of life.

Finally, the examination of feces from child 369B revealed no vitamin K content in the first 13 days of life, when it was exclusively breast-fed. After the child had been put on artificial feeding on account of the mother's mastitis, there was still no vitamin K in feces from the first five days after the change of diet, whereas considerable quantities were found in the subsequent samples.

The importance of the form of nutrition to the content of vitamin K in feces as here demonstrated agrees with what is already

Table 6.

Determinations of vitamin K in feces of children of various ages.

Case record No.	Age	Diet	Dry substance per cent	Lipid per cent	Vitamin K units per gram		Number of chicks
					lipid	dry substance	
666/41	2 ½ months	Artificially fed	16.0	2.56	8000	200	2
29/42	4 ½ months	»	25.2	1.62	10000	160	4
667/41	10 months	»	26	1.83	6000	110	2
B.	14 months	»	15.8	5.37	2500	130	2
H.	3 years	Full diet	19.4	7.64	1500	120	3
17/42	5 years	»	30.3	4.45	1500	70	1
40/42	5 years	»	20.7	3.32	15000	500	4
670/41	9 years	»	16.3	3.16	2500	80	2
112/42	11 years	»	23.5	3.29	8000	250	4

known of the influence of diet on the nature and number of bacteria in the intestine.

Artificially fed children usually avoid a prothrombin fall in the first days of life; whether or not this is due to the more abundant intestinal flora, as has been assumed (11), is still an open question. It is possible that the difference in prothrombin may be explained solely by the fact that breast-fed children receive a smaller quantity of vitamin K through their food than artificially fed children. (6)

Determination of Vitamin K in Feces of Children from 2½ Months to 11 Years.

As we had found great differences in the vitamin K content in the feces of new-born children and of adults, we determined the content in the feces of children of various ages in order to ascertain whether older infants and bigger children also differ from adults in this respect. As was the case when examining the adults, these children were kept on a diet low in vitamin K for three days before the examination. The children include some normal individuals and others with affections not concerned with the alimentary tract. The results are shown in Table 6.

It appears from this table that there is no correlation between age and the vitamin K content in feces. The values are of the same order as for adults but they show a somewhat greater variation. The results thus show that even from the age of two months the vitamin K content in feces is of the same order of magnitude as that for adults.

Discussion.

An ordinary mixed diet including milk and butter, but with no large quantity of green vegetables, will contain probably 2000—4000 Dam-Glavind units of vitamin K per day, and a diet without milk, butter and greens will contain much smaller quantities. The quantity of vitamin K in feces from normal adults is found to be 20—40 units per gram fresh feces. If the daily quantity of feces be put at 200 grams, this will mean a daily excreted quantity of vitamin K of 4000—8000 units. The figures thus show that a consider-

able synthesis of vitamin K takes place in the intestinal tract of adults. Whether or not this synthesis is of any physiological significance to the supply of vitamin K to man is a question that cannot be decided on the basis of the present investigation. Nevertheless, the rare occurrence of alimentary K-avitaminosis may point in that direction.

The above remarks can also be applied to older children.

The significance of this synthesis of vitamin K in the intestinal tract of new-born children will be discussed in a subsequent paper.

Summary.

1) The content of vitamin K in feces has been determined in feces from normal adults, pregnant women, new-born children and older children by means of Dam & Glavind's curative method. In all those examined, with the exception of breast-fed children, we found quantities of vitamin K corresponding to or exceeding the content of vitamin K of the ingested food.

2) In feces from normal adults receiving a diet deficient in vitamin K we found quantities of vitamin K from 1000 to 3000 Dam-Glavind units per gram feces-lipid, corresponding to about 20—40 units per gram of fresh feces. There is reason for assuming that this quantity results mainly from the intestinal bacteria.

3) In feces from normal pregnant women we found vitamin K values of the same order of magnitude as in feces from normal, non-pregnant adults.

4) In feces of new-born breast-fed children it has not been possible to demonstrate the presence of vitamin K by means of the method employed.

5) In feces of new-born artificially fed children vitamin K was found in almost every case, as a rule in much smaller quantities than those found in feces from adults and older children.

6) In feces of children of ages from 2 ½ months to 11 years we demonstrated the constant presence of vitamin K in quantities of the same order of magnitude as the quantities found in feces from adults.

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Investigations into the Cause of the Physiological Hypoprothrombinemia in New-born Children.

IV. The Vitamin K Content of Woman's Milk and Cow's Milk.¹

By

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(Submitted for publication June 22nd, 1942),

There is only one report published on the vitamin K content of woman's milk: Tage-Hansen found no demonstrable amounts of vitamin K in three specimens, and in a fourth he found approximately $\frac{1}{3}$ Dam & Glavind units per ml. As a vitamin K requirement of new-born infants of 0.5—1 Dam-Glavind-units per gram body-weight was assumed, woman's milk was not considered to be an essential source of vitamin K. In the meantime later investigations of Sells, Walker and Owen showed that a daily administration of vitamin K, of an order of magnitude 0.001 mg given intramuscularly in the form of 2-methyl-1-amino-4-naphtol equal to 15 Dam-Glavind-units, or 0.005 units per gram body-weight, would prevent the usual fall of prothrombin in the blood during the first week of life. This is confirmed by Larsen who has shown that the requirement is about 75 units of vitamin K when given per os in the form of Sodium-2-methyl-1.4-napthohydroquinone-disuccinate. He also found that the first days' fall in protrombin could be prevented by the administration of sufficiently large amounts of woman's milk. More comprehensive investigations into the milk's vitamin K content

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than the above seem to be of interest to elucidate the causes of the physiological hypothrombinemia in new-born infants.

Procedure.

Dam & Glavind's curative chicken test was used to determine the amount of vitamin K in milk specimens. The specimens were stored in a refrigerator at 0° C. until determination. At the beginning of the experiment the chickens weighed approximately 150 grams, and on account of the material's poor vitamin K content, they were given as much milk as possible through a stomach-tube, that is to say 30 to 40 ml per day for three days.

As it was found questionable whether the chickens could utilise such large quantities of milk, in four instances, where there was a sufficiently large amount of milk, it was divided into two equal portions. One portion was administered as usual as whole milk, while of the other portion, only the milk fat separated by centrifugation were given. In every instance the effect of the two specimens was found to be the same. This suggests that the vitamin K is found in the milk fat, as might be expected, the natural vitamin K being fat-soluble. Further it suggests that the chickens are able to utilise vitamin K equally well both from large amounts of whole milk and corresponding quantities of milk fat.

The material used in this experiment consists of cow's milk, and of woman's milk derived from women at various dates after delivery.¹

Vitamin K content in cow's milk.

The cow's milk investigated was obtained fresh from the dairy during the months from December to March. It contained about 4 per cent fats. The results appear in Table 1, in which is shown the prothrombin content in the chickens' blood before and after three days of milk feeding, in terms respectively of $\frac{1}{R_1}$ and $\frac{1}{R_2} \cdot \frac{1}{R}$ expresses the chickens' prothrombin value in relation to the normal, the normal value being $\frac{1}{R} = 1.0$. Further, in this table is shown the number of cubic millimetre of milk given per gram chicken-weight daily (cubic millimetre per gram per day).

¹ Our thanks are due to Professor E. Hauch, M. D. and to Professor E. Rydberg M. D. for the permission to examine mother's milk from their departments.

Table 1.
Determination of vitamin K in cow's milk.

Date on which milk was obtained from the dairy.	Cubic millimetre milk per gram chicken-weight per day.	$\frac{1}{R_1}$	$\frac{1}{R_2}$
4th Dec.	66	00.9	0.56
do.	38	0.03	0.04
20th Dec.	203	0.08	0.44
do.	53	0.08	0.09
do.	36	0.05	0.04
13th Jan.	92	0.07	0.17
16th Mar.	148	0.04	0.62
do.	200	0.02	0.10
17th Mar.	147	0.04	0.07
21st Mar.	160	0.08	0.24
do.	167	0.09	0.05

By means of the values found, a curve showing the increase of $\frac{1}{R_1}$ in relation to the amounts given was drawn. By comparig this curve with a corresponding curve drawn on the basis of experiments made with a standard substance (dried spinach) the vitamin K content in the cow's milk investigated is calculated to be 2 Dam-Glavind-units per ml. The results suggested that the content fluctuates considerably, as some tests caused no increase in $\frac{1}{R_1}$, while others caused a rise of $\frac{1}{R_1}$, corresponding to a vitamin K content of about 4 Dam-Glavind-units per ml.

Vitamin K content in woman's milk.

The woman's milk investigated was derived partly from lying-in patients in the departments of obstetrics of the Rigshospital, and partly from wet-nurses supplying milk to the department of peditrices of the Rigshospital.

The milk specimens with one exception (Case Record No. 1773 A) were taken on three consecutive days, and given to the chickens as fresh as possible. As a rule there was only sufficient milk for one chicken from each mother, and in a few cases it was necessary to use milk from several mothers in order to obtain the necessary quan-

tity. Thus no proper standardisation of the individual milk specimens' vitamin K content has been carried out; nevertheless the results make it possible to form an estimate of whether they are more or less abundant in vitamin K.

The results are seen in Table 2. In this table is stated the number of days after delivery on which the milk specimens were taken. Some of the mothers received immediately before delivery 5 mg of a water soluble vitamin K preparation per os. This is indicated by + or 0 in the table. Cubic millimetre of milk per gram chicken-weight per day, $\frac{1}{R_1}$ and $\frac{1}{R_2}$ signify the same as in Table 1. To facilitate the survey, it is indicated in the final column by 0, + or ++, whether it has been impossible to show the effect of vitamin K on the chickens' prothrombin content, whether the result indicated a rather poor amount of vitamin K, or whether there is probably a larger amount to be found.

It can be seen in this table that there is a noticeable variation in the vitamin K effect of the milk specimens. To determine the average vitamin K content in the milk, the entire material was treated as a whole and by the same method as used in the determination of vitamin K in cow's milk. Thereby we have graphically calculated an average vitamin K content of 0.5 Dam-Glavind-units per ml in the investigated woman's milk. In a number of specimens there was no vitamin K effect while other specimens indicated a content of up to 2 Dam-Glavind-units per ml.

The values found give no certain basis for assuming that the vitamin K content in the first days' milk is different from that found at a later date. Neither has it been possible to demonstrate in the milk specimens, which, at the earliest, are derived from the patient on the third day, the effect of administration of vitamin K shortly before delivery.

In five of the cases where the milk was derived during the first week after delivery, and where vitamin K was not administered to the mother or child, prothrombin determination was made on the child on the first, third and eighth days. No correlation between the infants' prothrombin variations and the vitamin K content of the mother's milk was found. (See beneath under »Discussion»).

It was further investigated whether the administration of a water soluble vitamin K to the mothers after delivery influenced the

Table 2.

Determination of vitamin K in woman's milk.

Case Record No.	Days after delivery	Vitamin K to the mother before delivery	Cubic millimetre milk per gram chloride-weight per day	$\frac{1}{R_1}$	$\frac{1}{R_2}$	Vitamin K in milk.
1789 B/41	2—3—4	0	139	0.02	0.03	+
1760 B/41	3—4—5	0	129	0.03	0.29	+
1728 A/41	3—4—5	+	121	0.02	0.19	+
1762 B/41	3—4—5	+	102	0.03	0.09	+
1763 B/41	3—4—5	0	218	0.03	0.15	+
1785 B/41	3—4—5	0	91	0.03	0.05	+
1765 B/41	4—5—6	0	149	0.07	0.32	+
1762 B/41	4—5—6	+	177	0.04	0.05	+
1789 A/41	5—6—8	0	163	0.05	0.01	0
1801 A/41						
1809 A/41						
1667 A, 1715 A, 1717 A, 1711 A, 1693 A, 1679 A/41	5—19	0	253	0.03	0.07	+
1813 B/41	6—7—8	0	66	0.04	0.03	0
1773 A/41	10	0	112	0.04	0.07	+
1773 A/41	11	0	135	0.05	0.06	+
314 A/42	10—11—12	0	170	0.01	0.05	+
319 A/42	14—25—26	+	110	0.05	0.04	0
250 A/42						
282 A/42	19—20—21	+	136	0.04	0.04	0
do. A/42	19—20—21	+	125	0.02	0.02	0
do. A/42	21—25—26	+	116	0.06	0.03	0
do. A/42	21—25—26	+	130	0.07	0.05	0
1642 A/41	25—26—27	+	120	0.01	0.12	+
Wet-Nurse T.	35—36—37	0	175	0.03	0.03	0
Wet-Nurse G.	43—44—45	+	128	0.06	0.04	0
do.	43—44—45	+	164	0.08	0.05	0
do.	43—44—45	+	133	0.08	0.07	0
do.	43—44—45	+	207	0.07	0.07	0
Wet-Nurse N.	105—106—107	0	157	0.03	0.23	+
do.	114—115—116	0	160	0.08	0.04	0
Wet-Nurse A.	270—271—272	0	246	0.02	0.53	+
do.	275—276—277	0	157	0.03	0.13	+

Table 3.

Determination of vitamin K in woman's milk after previous ingestion of vitamin K.

Case Record No.	Preparation.	Cubic millimetre milk per gram chicken-weight per day.	$\frac{1}{R_1}$	$\frac{1}{R_2}$
607/42	Sodium 2-methyl-1.4-naptho-hydroquinone-dissuccinate.	190	0.01	0.20
607/42		117	0.01	0.12
636/42		127	0.01	0.14
616/42		75	0.01	0.05
677/42		109	0.05	0.19
680/42	Sodium 2-methyl-1.4-naptho-hydroquinone-disulphate.	82	0.07	0.11
683/42		86	0.05	0.17
684/42		139	0.02	0.07
689/42		113	0.05	0.15

milk's vitamin K content. Four mothers were given 10 mg 2-methyl-1.4-napthohydroquinone-dissuccinate per os daily for three days, in each case 24 hours before the milk specimens were taken, and five mothers were given 10 mg Sodium 2-methyl-1.4-napthohydroquinone-disulphate. The results are shown in Table 3.

The results show that the vitamin K content in woman's milk after the foregoing administration of vitamin K is higher and more uniform than is usual in woman's milk. A graphic calculation of the average vitamin K content shows a concentration of approximately 2 Dam-Glavind-units per ml.

Discussion.

Infants, exclusively nourished by mother's milk, consume a quantity of milk during the first week of life, rising from 10 to 20 grams in the first twenty-four hours to several hundred grams on about the seventh day. Thus, as mother's milk contains from 0 to 2 vitamin K units per gram, infants obtain daily through the milk, vitamin K in quantities which can vary from almost nothing up to 400 units. It might be expected to find correlation between the vitamin K content in the mother's milk and the infant's prothrombin variations. As mentioned above, this could not be demonstrated, possibly because no account was taken of the total amount of milk which the infants had consumed, and further, because the

milk's vitamin K content was determined only in some few specimens and not in the total quantity of milk produced during the first week.

As mentioned above, it has been shown that the infant's vitamin K requirement in the first week of life is about 75 units daily, by peroral administration; it must therefore be concluded that the vitamin K supplied through the milk plays an important perhaps the most essential role in supplying the infant's vitamin K requirement. As the vitamin K concentration in woman's milk is shown to be very variable, and as the quantity of milk consumed by the infant especially in the first days varies very considerably, it is probable that variations in the amounts of vitamin K in the infant's food are an important cause of the pronounced prothrombin variations found in the first week of life.

Summary.

1. Vitamin K content, is determined in cow's milk and woman's milk by Dam & Glavind's curative chicken method.

From 0 to 4, an average of 2 units per ml is found in cow's milk from the winter half-year. From 0 to 2, an average of 0.5 units per ml. is found in woman's milk. After ingestion of water soluble vitamin K to the mother, the content rises to approximately 2 units per ml.

2. The quantities found must be assumed to play an important part in the provision of the infant with vitamin K in the first week of life.

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Sewage as a carrier and disseminator of Poliomyelitis Virus.

By

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Part I.

Searching for poliomyelitis virus in Stockholm sewage.

Contents:

- A. Observations made in the first test.
- B. Origin of the isolated poliomyelitis virus.
- C. Observations made in the second and third tests.
- D. Review and discussion.

Since the methods for detecting the virus of poliomyelitis in intestinal contents have been more serviceable than before, investigators in various countries have been able to report during the last two or three years that they have discovered the virus in human stools derived from both typical and abortive cases of infantile paralysis and from convalescents recovering from this disease. In the course of an epidemic of poliomyelitis in Stockholm in the autumn of 1939 it was possible at our institute, as stated elsewhere,¹ in the same test material in such case where it was collected during the earlier stage of the disease, to establish the pre-

¹ C. Kling, »Some features of recent experimental poliomyelitis research», Sv. Läkaresällskapets förhandlingar, 1941, 25, 1954.

sence of the specific agent at such a high rate that there was cause to assume that its elimination through the intestine is a regular phenomenon. It is quite natural that under such circumstances one expects, that during an epidemic the *sewage* may be contaminated. The question is whether the poliomyelitis virus is able to keep alive in this medium and if it enters in such a quantity that its presence can be determined by means of the ordinary tests. The first answer to this question was obtained by an account of the experiments which the American investigators Paul, Trask and Culotta (subsequently in co-operation with our Swedish colleague S. Gard) had carried out in the course of urban epidemics of infantile paralysis in the U. S. A. during the summer of 1939.¹ In reality, these investigators succeeded in demonstrating at three places where the epidemic raged (in the City of Charleston, in Detroit, in Buffalo City) the existence of the virus in sewage. As soon as we were informed of this discovery, it seemed to us important to get it verified. Such an opportunity presented itself in the autumn of 1939 during an epidemical manifestation of the disease in Stockholm.

We succeeded also pretty soon in registering a *positive* result. In a preliminary form this was communicated by M. Levaditi to the Académie de Médecine in Paris in, April, 1940, with ensuing comments.² The detection of the virus of poliomyelitis in Stockholm sewage was also reported during the autumn of the same year to the Swedish Board of Health.³

After this period we continued to try to elucidate the further fate of the poliomyelitis virus in the Stockholm sewage. The experimental and epidemiological observations made previously and subsequently have induced us during the past year to commence investigations into the conditions of life of poliomyelitis virus *outside* the human organism. In the ensuing we shall render an account of the results of our investigations hitherto achieved, both in the first and in the second respect.

¹ John Paul, James Trask and S. Culotta, 'Poliomyelitis virus in urban sewage', *Science*, 90, 258, Sept. 1939.

John Paul, James Trask and Sven Gard, 'Poliomyelitis virus in urban sewage', *Journal Exp. Med.* 1940, 71, 765.

² C. Kling, 'Sur la présence du virus poliomyélique dans les eaux d'égout', Note présentée par M. G. Levaditi, *Bull. Acad. Médecine* 1940, 122, 335.

³ C. Kling; Report to the Swedish Board of Health, Stockholm, 16 Sept. 1940.

I. Searching for Poliomyelitis virus in Stockholm sewage.

A. *Observations made in the first test.*

In the year 1939 there occurred in the capital, to judge from reports received, altogether 88 cases of poliomyelitis, of which 73 were *with* and 15 *without* paralysis, the vast majority — numbering 67 — during the months of August, September and October. In the previous year there was practically a total absence of the disease (only a few sporadic typical cases or a small number of probably abortive cases) and during 1940, until the end of August, not a single case of disease of this kind had been reported. It was thus clear that we had to do with an epidemic outbreak of poliomyelitis in the capital in the year 1939. The cases of the disease were fairly evenly distributed over all parts of the city, without any real tendency of forming foci (see accompanying map, fig. 4, of the Stockholm sewer-net on which also the cases of poliomyelitis are marked). The disease was of a relatively mild character and ended in only a few cases in death.

For reasons which in the ensuing description of the Stockholm sewer system will be stated more particularly, there was selected as a site for collecting a specimen of sewage a regulation chamber (see fig. 4, at b) situated near Tegelbacken, or very close to the recipient used by the city. Here were taken, on the 11th October, 1939, under sterile precautions, 10 litres of sewage, which were allowed to sediment for a week in the refrigerating room of the laboratory. From the bottom layer, which had been strongly cloudy, was transferred by means of a syphon approximately 1 litre of the liquid to sterile containers, which were placed in the cold. On account of other urgent work the test material could not be dealt with until the 12th December, i. e. *after 2 months' storage*, a circumstance which, as we shall see from the ensuing, became of importance for judging the question regarding the conditions of resistance of the poliomyelitis virus in the medium referred to. For enabling the inoculation of the material into the ordinary test-animal — the monkey — we used in principle the same method as that which of recent years in numerous cases we had employed for the inoculation of the

poliomyelitis virus from feces, i. e. shaking in ether for the purpose of getting them purified from banal bacteria¹ — a technique which had been inaugurated by Paul and Trask in 1938;² Here are the particulars of this experiment.

The sediment deposited during storage in the cold from about 6 litres of sewage, was diluted in sterile, distilled water and shaken for 8 hours to bring about a finely distributed suspension. Concentration of the liquid in a vacuum at a low temperature (about 7° C) to 100 cm³. After an admixture of sodium chloride in substance for attaining isotony and mixing with a double volume of ether agitating in the shaker for three hours.

For the animal test were used both the clear liquid (fraction A) resulting from a double centrifugation, the first a slight one, the second in a winkel centrifuge at about 3500 R. P. M. for 60 minutes, and the sediment suspended in 60 cm³ of physiologic salt solution (fraction B). Both fractions were submitted to new ether treatment in order to deprive them, as far as possible, of banal bacteria (for altogether 9 respectively 18 hours).

After that began the customary test of the two liquids for their poliomyelitis producing capacity.

On the 18th Dec., 1939, *Macacus rhesus* V. T. 49 is given 30 cm³ of fraction A peritoneally and 1 cm³ neurally (in one n. ischiadicus). The animal, which was under observation until the 8 Jan., 1941, or 21 days, without displaying any paralytic symptoms, was then sacrificed. In the necropsy nothing abnormal noted in the internal organs. *Blood-culture*: no growth. Histologically the nervous system looked quite normal.

On the following day, the 19th Dec., *Macacus rhesus* V. T. 51 inoculated peritoneally with 60 cm³ of fraction B and 1 cm³ neurally (in one n. ischiadicus). On the 6th Jan., 1940, i. e. after 18 days, the monkey is found to be paretic in both arms. The same status during the next three days, for which reason the animal is sacrificed. In the autopsy the mesenteric, inguinal and axillary lymph nodes are found to be greatly enlarged and red, but otherwise the internal organs are without any remark. *Blood-culture*: no growth.

At the microscopical examination of the neuraxis there is stated, as fig. 1 shows, the presence of *wide-spread and very intense poliomyelitic lesions* (in the hypothalamus, the floor of the fourth ventricle, the medulla and in the grey matter of the cervical and dorsal cords; also in the grey matter of the lumbar cord perivascular infiltrations are noticed but the neuronophagia are here sparse).

On the 22nd Jan., 1940, a first passage is made, in that a suspension of the neuraxis from monkey V. T. 51, stored in the refrigerator, is inoculated into *Macacus rhesus* V. T. 51-A cerebrally and peritoneally. This animal

¹ C. Kling, G. Olin, J. H. Magnusson et S. Gard, Acta Medica Scandinavica, 1939, 111, 6.

² C. Kling, Report to the Swedish Board of Health, Stockholm 10 Sept., 1940.

³ Trask, Vignee et Paul, Journ. Amer. Med. Ass. 1938, 111, 61.

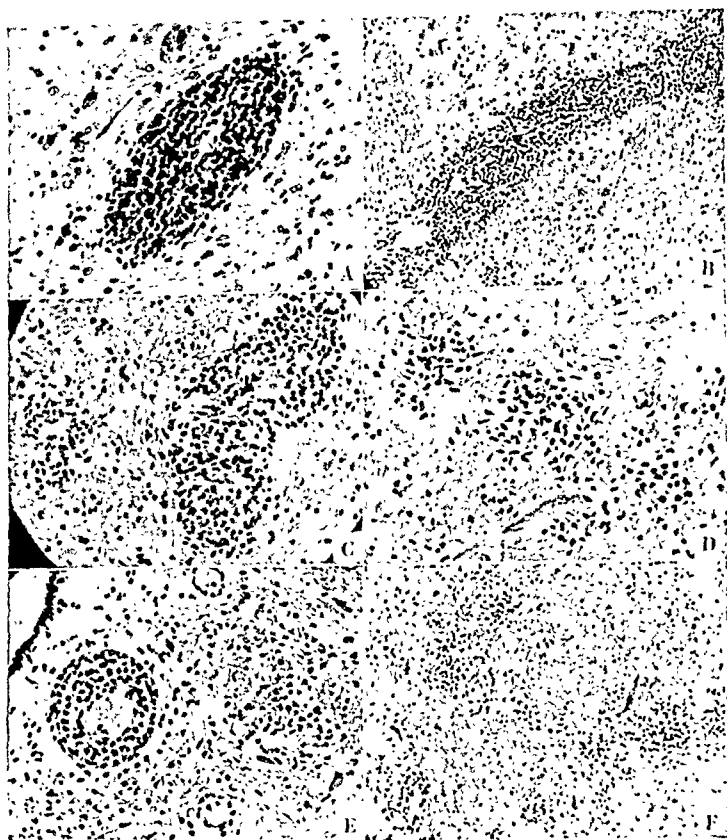


Fig. 1. *Macacus rhesus* V T 51 with paralytic poliomyelitis.

- A. Hypothalamus showing mighty perivascular infiltrations.
- B. Floor in the fourth ventricle. Same changes.
- C. Medulla. Same changes.
- D. Cervical cord, showing neuronophagia in the anterior horn.
- E. Dorsal cord with perivascular infiltrations and neuronophagia (right).
- F. Cervical cord, slight magnification. Note the numerous foci of neuronophagia.

shows on the 8th Feb., or after 18 days, clinical symptoms of poliomyelitis (tremors, paretic in both arms and one leg); sacrificed on the next day. The nervous system reveals microscopically typical and intense poliomyelitic lesions, still more advanced than in the primarily infected monkey.

With the neuraxis from monkey V. T. 51-A *Macacus rhesus* V. T. 51 C, is infected in the same manner as monkey V. T. 51-A. On the 12th March, or 14 days after inoculation, the animal falls ill with typical symptoms of poliomyelitis (complete paralysis of the left hand, paresis in the other extremities) and is sacrificed. Typical and severe changes in various parts of the neuraxis present.

From these experiments it is apparent that we have succeeded in isolating the virus of poliomyelitis in a sample of sewage collected in Stockholm in the course of a minor epidemic of infantile

paralysis. The virus isolated was sufficiently infectious to produce in the monkey (*Macacus rhesus*) a typical experimental disease, which could be transferred from animal to animal.

But the experiment also gives us clarity about the ability of the poliomyelitis virus to keep alive under certain conditions in a medium of the said kind. For the aforesaid reason the test material was inoculated first after two months' storage at a temperature of $+4^{\circ}\text{C}$. From this fact can be drawn the conclusion that *this etiologic agent can retain its virulence in sewage at a low temperature for quite a long time*. It would, of course, have been interesting to deal further with this question, but the necessary supply of monkeys proved an obstacle to this, and we had therefore to adjourn the further study of this subject to a more favourable opportunity. Earlier experimental investigations have, however, supplied us with certain knowledge regarding the question of the resistance of poliomyelitis virus in a water-medium of another kind, to which we shall revert when dealing with the epidemiological significance of our finding.

But even from a *technical* point of view it is of importance to know as exactly as ever possible how long sewage contaminated with poliomyelitis virus retains its virulence during suitable storage. In the sedimentation of the sewage, which is allowed to precede the inoculation into the monkey, the concentration of its fecal substances is increased. By reason of earlier experiences there is cause to suspect that, at least in some cases, the poliomyelitis virus may be destroyed during contact with the said substances. Already in 1931 Levaditi, Kling and Lépine¹ showed that merely a contact with *monkey feces* is able to diminish, aye, even to annihilate the virulence of a spinal cord-suspension. Kling, Olin, Magnusson and Gard² tried, in 1938, to further clear up this problem. They found that a virulent human stool (derived from an abortive case of poliomyelitis, and after collection stored under ether for 12 days) in repeated tests, carried out after 53, 152 and 190 days had lost their specific pathogenicity. In virtue of increased experience gained by us during the 1939 Stockholm epidemic we know now that one has to do with individual variations in regard to the resistance of poliomyelitis virus in human fecal matter. For we saw its virulence retained after 50, aye, even after 105 days' storage under a layer of *ether* in the cold. (In the ensuing we shall revert in detail to this question). The preceding remarks may perhaps be sufficient to illustrate that for the time being it will be most prudent, as also Paul, Trask and Gard³ recommend, to allow the shortest possible interval to elapse

¹ Levaditi, Kling et Lépine, Bull. Acad. Med. 1931, 105.

² Kling, Olin, Magnusson et Gard, Acta Medica Scandinavica, 1939, 112, 6.

³ Loc. cit.

between the collection of the sewage and its testing for the presence of poliomyelitis virus.

Another detail of technical interest may also call for some comments. In spite of repeated and lengthy shaking with ether we did not succeed in getting the clear liquid or the sediment obtained by means of centrifugation perfectly free from bacteria. We were, therefore, forced to give up the *cerebral* route of inoculation (fearing secondary infection), and we had in both cases to administer the material *peritoneally* and *neurally* (in one n. ischiadicus). The method led in spite of this in the one test animal, viz. monkey V. T. 51 (inoculated with the sediment suspended in physiologic saline solution) to a *positive* result, while the monkey V. T. 49, inoculated with the clear liquid, escaped infection. How shall we explain these varying results? Have we had to do with a different receptivity in the two test animals or was the poliomyelitis virus present in a higher concentration in the sediment than in the clear liquid? It is impossible to give a precise answer to this question, to judge merely from these two solitary experiments. It may in this connexion be worth mentioning that one succeeds relatively easily in getting the liquid obtained by prolonged centrifugation of a fecal suspension, with subsequent agitation with ether for a longer or shorter period, perfectly free from bacteria. Such a liquid can be inoculated both *cerebrally* and *peritoneally*. We have been able, in the autumn of 1939, to demonstrate virulence in several liquids of that kind derived from cases of poliomyelitis. It is clear that the virus, in spite of the strong centrifugation, is kept suspended in the liquid in sufficient quantity to manifest its presence in the test experiment.

As has been said in the preceding pages, the strain of poliomyelitis virus isolated from Stockholm sewage could be passed through three *rhesi* (V. T. 51, V. T. 51A and V. T. 51C). The experimental disease induced in these animals was of a clinically and anatomically typical character. Other passages made with this strain gave further information about its properties.

On the 22nd Jan., 1940, we prepared a suspension of the swollen mesenteric, inguinal and axillary lymph nodes from monkey V. T. 51 stored in glycerol (the neuraxis of this animal was fully virulent as proved by the first passage accomplished with it; see above). The suspension was given to *Macacus rhesus* V. T. 51 B by cerebral and peritoneal injections. This monkey remains in spite of careful observations perfectly free from paralytic symptoms until the 15th Febr., during 29 days, when it was sacrificed for histological examination. As illustrated in fig. 2, there are present in the inoculation area wide-spread glial reactions around the blood vessels, perivascular infiltrations in the walls of the ventricles, in the choroid plexus, and the pons matter. In addition to these changes one can see neuronophagia, even if sparsely, in certain segments of the spinal cord and also the patchy perivascular meningitis in several levels of *cerebrum*, *pons*, and of the spinal cord.

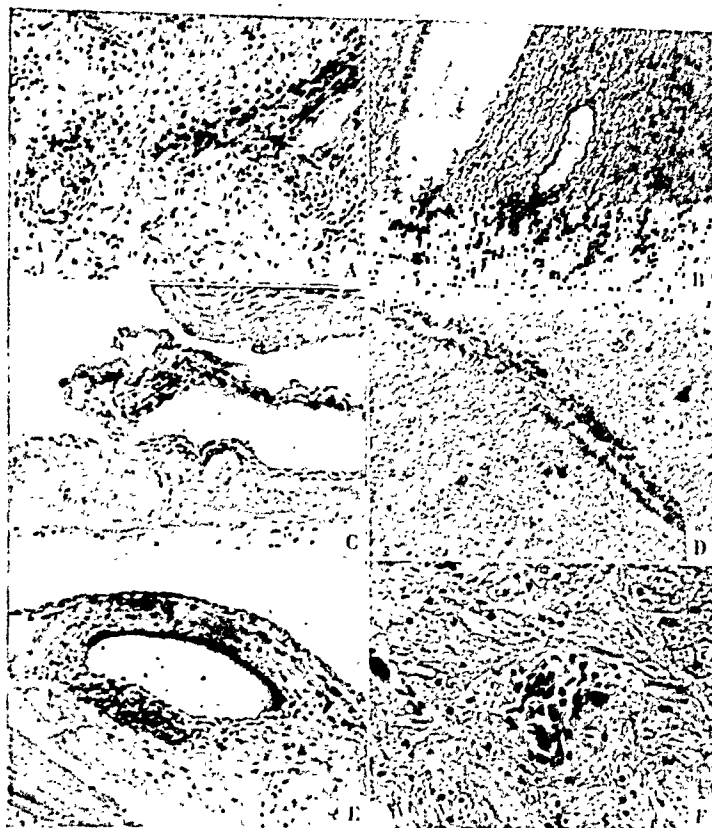


Fig. 2. *Macacus rhesus* V T 51 B with abortive poliomyelitis.

- A. Inoculation area (in the vicinity of the anterior horn of one of the lateral ventricles), showing perivascular glial infiltrations.
- B. Wall of the inferior horn of one of the lateral ventricles with a perivascular infiltration.
- C. Pons. Mononuclear perivascular meningitis at its ventral side.
- D. Pons, showing a perivascular infiltration.
- E. Cervical spinal cord with perivascular infiltration in the pia.
- F. Cervical spinal cord. Note the focus of neuronophagia in the grey matter.

On the 1st April, 1940, *Macacus rhesus* V. T. 51 D was infected with a spinal cord suspension from monkey V. T. 51 C (the third animal in the serial passages with virus V. T. 51) cerebrally and peritoneally. The animal under observation until the 22nd April without displaying any morbid disturbances. Sacrificed on this date, i. e. 22 days after inoculation. Histologically the optic thalamus, the roof of the fourth ventricle and the grey matter in several segments of the spinal cord reveal lesions typical of poliomyelitis (perivascular and focal infiltrations, partly consisting of hypertrophic gliacells, but also characteristic neuronophagia in the anterior horns, see fig. 3).

We have previously in not rare cases since the start of the last great epidemic of poliomyelitis during the year 1936, been given irre-



Fig. 3. *Macacus rhesus* V T 51 D with abortive poliomyelitis.

- A. Thalamus with mighty perivascular infiltrations.
- B. Roof of the fourth ventricle, showing light perivascular infiltrations.
- C. Lumbar spinal cord, showing a perivascular infiltration in the pia.
- D. Lumbar spinal cord. Perivascular infiltrations near the central channel.
- E. Lumbar spinal cord. Note the focus of neuronophagia in the anterior horn.
- F. Lumbar spinal cord, showing a mighty glial infiltration in the grey matter.

futable proofs that experimental poliomyelitis can occur as an *inapparent* infection, which diagnosis can only be made by the histological examination of the nervous system. We have seen it make its appearance after inoculation with indubitable poliomyelitic material from human beings (spinal cord, lymph nodes), with intestinal content from typical cases of poliomyelitis and from abortive ones; we have observed it in the course of our serial passages carried out with typical strains of poliomyelitis virus¹ isolated from test material of the said kinds. We have now also been able to

¹ Kling, Olin, Magnusson et Gard, Loc. cit. p. 634.

C. Kling. »In search of poliomyelitis Virus in Drinking Water, The International Bulletin, Vol. A. 40: Infantile Paralysis, p. 166—172.

C. Kling, Report to the Swedish Board of Health, 10th September, 1940.

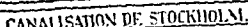
make similar observations in passages accomplished with the strain of poliomyelitis virus V. T. 51 isolated from Stockholm sewage. Of the five monkeys that had been infected with this strain, and whose histological lesions have been commented in the preceding, the experimental disease has in two of them passed without any noticeable clinical symptoms. We shall in the ensuing, when the question arises about persistence of poliomyelitis virus in Stockholm sewage, communicate a third observation of the same kind:

B. *Origin of the isolated poliomyelitis virus.*

The question arises now: Whence was the poliomyelitis virus derived, which has been isolated from Stockholm sewage? In order to elucidate this question, it is necessary to render an account of certain circumstances of importance in this regard. First, some orienting information about the Stockholm sewer-system in its present condition.

The Stockholm sewer system is at present in process of reconstruction along fully modern lines. After having previously allowed the main sewers to empty direct into the recipient — Riddarfjärden, Norrström, and the Baltic — i. e. working along the so-called perpendicular system, a departure is now being made to the *combined* system with common sewers for surplus sewage (accruing during increased precipitation) and waste-water of different kinds and with the main sewers emptying into intercepting sewers, which join at sewage works in course of construction at Henriksdal. After mechanical and chemical treatment at these works, the sewage will empty into the Baltic, just below the Danvik Hospital. On the accompanying map we have tried to illustrate the most important parts of the sewer system, for which reason it is not necessary to enter into details. The intercepting sewers have for the greater part come into operation, but since the sewage-works have not yet been finished, the collected sewage is allowed, after the junction of the intercepting sewer in the south with the main sewer coming from Brännkyrka, to empty provisionally into the Baltic close to the steps at Tegelviken (See at e).

During the reconstruction of the sewer system now progressing, it has, of course, not been altogether possible to avoid the drawbacks attached to the old system. Thus there has, by way of example, not been time to start on the planned intercepting sewer between Kungsholmen and the Rosenbad Park (between a and c on the map), for which reason the sewage from some of the northern parts of the city had to be conducted direct into Riddarfjärden, through a divers' sewer running underneath Klarasjö Lake. During some months in the autumn of 1939 (between the 3rd October and



14th November), or during the poliomyelitis epidemic raging, the intercepting sewer, which runs between the regulating chamber near Rosenbad (see map at c) and the pumping station near Karl XII's Square (the largest of the 4 pumping stations of the system) has been interrupted on account of the work of installation in progress. The sewage from the Norrmalm drainage area was during the said period carried off through the sewer at Vasagatan and through its extension — an old pipe running through the well (b) near Tegelbacken — out into the recipient. Only a minor quantity of the sewage from the said drainage area was diverted on this occasion through the main sewer, which, starting from the sewer at Vasagatan, empties into the regulating chamber at Rosenbad and then through its storm overflow out into Norrström (see map at c).

From this description of the Stockholm sewer one can draw the definite conclusion that the specimen of sewage examined was only derived from the *Norrmalm drainage area*. This area lacks connexion with the recipient, into which the outlet from the city's Isolation Hospital empties, viz. Brunnsviken, a water-way not directly con-

Table 1.

Cases of poliomyelitis within the Norrmalm drainage area
(throughout the year 1939)

Number of cases reported to the Board of Health	Clinical types	Date of falling ill	Date for reception at Isolation Hospital	Stay at home between falling ill and reception at Hospital	Time lapsed between falling ill and collection	Possible source of infection
2.	with paralysis	10/1	15/1	5 days	10 months	?
7.	with "	20/1	1/3	8 "	7—2/3 "	?
8.	with "	23/2	4/3	9 "	7—1/2 "	?
4 a.	without "	12/4	13/4	1 "	6 "	?
17.	with "	15/8	31/8	16 "	50 days	?
24.	with "	22/8	14/9	23 "	50 "	?
26.	with "	23/8	26/8	3 "	49 "	?
44.	with "	16/9	21/9	5 "	27 "	presumable
10 A.	without "	23/9	27/9	4 "	18 "	"
64.	with "	9/10	12/10	3 "	2 "	"
69.	with "	19/10	20/10	1 "	— "	excluded
73.	with "	7/11	7/11	½ "	—	"

nected with the recipient proper — the outlet of Lake Maelar into the Baltic. It may further be stated that an immediate disinfection of the stools is made before they are emptied into the drains of the hospital. We may thus with *absolute certainty exclude the assumption that the isolated poliomyelitis virus emanated from the patients under treatment at the Isolation Hospital.*

If we assume that the poliomyelitis virus which occurred in the Norrmalm sewer system had been derived from human sources of infection, these sources must have existed within the drainage area. Approximately 100,000 persons are living within this part of the city. As we can see from the attached map, there had during the whole of 1939 occurred in this urban area 12 cases of poliomyelitis, of which 10 *with* and 2 *without* paralysis. Four of the cases occurred during the first 4 months of the year, the remaining eight during the period August-November.

In order to illustrate how many of the 12 cases could constitute the origin for the poliomyelitis virus isolated, they have been brought together in table 1, stating the type of the disease, date of falling ill, date for reception at the Isolation Hospital and the occasion of collecting the sample, and, finally, their supposed part as sources of contamination for the sewage on the occasion in question.

We see, then, first from this summary, that two of the cases (N:o 69 and 73) without any further ado can be excluded as sources of infection, inasmuch as they occurred on the 19th October and 7th November, respectively, or after the day on which the specimen of sewage was taken (11th October). One of the cases (N:o 17) was living within the southernmost part of the drainage area, and in such a site within the same that the stools from this case probably were discharged into the Rosenbad sewer (at c). Since, however, regurgitation of the contents of the sewer from the Rosenbad pipe to the sewer beneath Vasagatan on certain occasions cannot be excluded, we count also this case as a possible source of infection. As regards, again, six of the cases, it is seen that so long a period had elapsed between falling ill and the collecting of the sample (49 days — 10 months) that one must greatly question the possibility of these as *direct* causal factors¹ for the sewage contamination. Properly speaking, it is only three of the cases (44, 10 A and 64) which can seriously be included as presumable origin for the poliomyelitis virus isolated from the specimen of sewage — if by that one means an *immediate derivation* from the sick persons (2—27 days).

We see further from the table that 6 of the 10 cases, suspected as possible sources of infection, were lying in their homes before being removed to the Isolation Hospital, relatively a short time (3—5 days), the four remaining ones, on the other hand, for a longer period (respectively 8, 9, 16 and 23 days). During their stay at home the patients had certainly several times discharged intestinal excretions containing poliomyelitis virus into the sewer system in question. This excretion of virus has taken place during January, February and in April, and during the months of August, September and October. In another connexion it may be of interest that even after the time the specimen was taken, contamination of the sewer took place through fresh cases occurring, viz. two, during the months of October and November.

It is this that we know with certainty regarding the possibilities of the contamination of the sewage by poliomyelitis virus. It may

¹ In our investigations into the virulence of feces carried out during the Stockholm epidemic in the autumn of 1939, we found the positive specimens in 66.7 % to come within the 7 first days after falling ill, while those taken between the 8th and 25th day were positive only in 23.5 % of all those examined (in all 32 specimens). 17 respectively 20 days were the extreme limits for our positive tests registered during this epidemic. In exceptional cases, however, the virus can be excreted even for a longer period, to judge from investigations carried out in other quarters and on other occasions (Kling, Pettersson and Wernstedt in the year 1911, Lépine in 1938).

now be added: Contamination may also have been brought about through undiagnosed cases of poliomyelitis passing off *abortively* within the drainage area, and because of that not reported.

Of the 12 cases known within the Norrmalm drainage area, two had been comprehended as such forms of disease. Of the 88 cases reported during the year 1939 fifteen, i. e. 17 % of all, had been diagnosed as poliomyelitis *without* paralysis. This agrees pretty well with the statistics for the whole country¹ during the year in question. During that year our medical officers notified 614 cases of poliomyelitis, of which 131 *without* paralysis, or 21.4 %. It may also be mentioned that during the period 1936—1940 altogether 7555 cases of poliomyelitis were notified, of which 1163 without paralysis, forming an average of 15.4 %.

That some abortive case or other within the Norrmalm drainage area did not come under medical observation, is quite possible, *aye*, even probable, but in view of the anxiety and worry about the consequences of the disease, which in times of an epidemic always arise amongst our general public, and the eagerness in summoning a medical man at the slightest suspicion of the disease, we may assume that *such cases cannot have been particularly numerous*. No wide-spread sickness prevailed in the capital during the period here in question, for which reason we have also no cause to assume that any very large number of *un-reported* cases of poliomyelitis occurred. We are unable at our present stage of knowledge and with our hitherto diagnostic aids to present any bases for a possible presence of *healthy virus carriers*, but for epidemiological reasons it seems to us possible to assume that they had not been particularly numerous. If such virus carriers had existed in any large numbers, one should have been entitled to expect that poliomyelitis in a city like Stockholm, with its plentiful opportunities for contact between individuals, would have reached a much greater scope.

In view of the facts adduced in the preceding, i. e. the occurrence within the Norrmalm drainage area — before the collection of the sewage sample — of 10 cases of illness due to poliomyelitis during the year 1939, we are, however, able to make some general considerations and bring forward some theoretical remarks on how it might have been possible to disclose the presence of poliomyelitis virus in such a vast volume of sewage as the one here in question. First some summary items of information on the magnitude of this volume of water which we obtained from the respective authorities at

¹ As from the 1st September, 1936, our medical officers were obliged to report if the cases of poliomyelitis had passed off with or without paralysis.

the »gaturkontor» of the city. If one counts — which was done in the planning of the dimensions of the sewage works — with a quantity of waste-water running off at the rate of about 200 litres for each person and day (24 hours), we shall reach with a population of 100,000 persons as within the Norrmalm drainage area, a total quantity of 20,000 cubic metres of sewage, or 20 million litres. It is in this quantity of water that the stools discharged in the course of 24 hours are suspended.

Of this volume of sewage, amounting to 20 million litres, 6 litres (concentrated into 60 cm³ and injected peritoneally and neurally) had given rise to the manifest, but not fatal, poliomyelitis in the test-animal. If we estimate the quantity of virus introduced at *one* infective dosis, and presume that the virus has been equally distributed in the sewage, about 3 millions of infective doses per day (24 hours) would have passed through the Stockholm sewer system ($\frac{1}{6} \times 20$ millions). ¹

In our stool examinations during the Stockholm epidemic of 1939, we infected as a rule the monkeys with 2.5 grammes of fecal matter (about 50 cm³ of a centrifuged 5 percent fecal suspension) peritoneally and cerebrally, and in that manner we succeeded in about 40 % of the cases tested to isolate the poliomyelitis virus, which however in no case gave rise to fatal infection. We are, therefore, able to reckon approximately with *one* infective dose for 6—7 grammes of fecal mass (100 percent infection). If one reckons further with the excretion of 200 grammes of feces per person and day the consequence would be that a poliomyelitis patient during a certain stage of the disease discharges 30 doses per day (24 hours) infective for the monkey. If, in order to be on the safe side, one considers the ten cases of poliomyelitis within the Norrmalm drainage area as acceptable direct and only sources of infection, 20 million litres of sewage would thus during one day have contained 300 infective doses (10×30), but really there were, as is seen from the preceding remarks, only three cases of disease — viz. the freshest ones — which one need seriously have to deal with as likely origin for

¹ It may in this connexion be of interest to mention that Paul, Trask and Gard in the discussion of their discovery of poliomyelitis virus in the sewage of Charleston, theoretically estimated the quantity of virus that had passed through the site for collecting sewage specimens (the pumping station) at 18,000 effective doses per minute, which, if we convert the same into day-periods, amount to about 4 million doses — a remarkably good agreement with our own calculations.

poliomyelitis virus, altogether thus about 100 infective doses per day (of 24 hours).

Now, to judge from the result of the experiment with the Stockholm sewage, about 3 million infective poliomyelitis doses seem to have run through the sewer from the Norrmalm drainage area within the corresponding period. How shall one now explain this apparently divergent result of the calculations made? Can they be brought together under a common visual angle? We believe so. Two alternative possibilities present themselves, in our opinion.

The *one possibility* is, that the poliomyelitis virus has multiplied since leaving the sick individuals by means of the excrements. We are also able to get an approximate measure of the magnitude of this multiplication. It should with the said assumptions vary between 10,000 and 30,000 times, all according to whether one sues from 10 or 3 human sources of infection.

The *second possibility* is, that within the Norrmalm drainage area there had existed a considerably larger number of virus carriers than seems apparent from the occurrence of the observable, typical and abortive cases of disease. One asks, then, how many virus carriers would have been needed in order that, with the aforesaid premises (30 infective doses per individual and day), 3 millions of infective doses of poliomyelitis virus would have entered the sewage system? To this one can answer, that it may have required no fewer than 100,000 virus carriers, or in other words, the entire population of Norrmalm.

Of these two possibilities the latter seems to us very little probable, and this for epidemiological motives already mentioned. On the other hand, in our opinion the former possibility is much more easily acceptable, i. e., that the poliomyelitis virus, when it has once been eliminated into the sewage, has undergone a considerable multiplication whose magnitude one can only conjecture approximately. We shall in the ensuing revert to the conditions of this multiplication.

C. *Observations made in the second and third test.*

It seemed to us, of course, both from a practical hygienic and from a theoretical point of view, of interest to try and get clarity of how long the existence of poliomyelitis virus could be detected in

Stockholm sewage, especially since the epidemic of infantile paralysis had ceased. The two last cases in the capital fell ill, according to reports filed, on the 2nd and 7th November, respectively. Within the Norrmalm drainage area, which interests us experimentally, there had, after the collection of the specimen of sewage on the 11th October, occurred two cases, one with date of falling ill the 19th October, the other on the 7th November, both cases of a paralytic type. It is the last-mentioned date that interests us especially. The patient in question had been received at the Isolation Hospital on the same day. *As from the 7th November, 1939*, we are therefore able to reckon with a finish of the contamination of the Norrmalm sewage by poliomyelitis virus, at least from known human sources of infection.

On the 15th February, 1940, thus after fully three months had elapsed from the occurrence of the last case, we resolved to repeat the sewage tests from the same drainage area. We were then unable to make use of the same site of collection as the first time, viz. the regulation chamber at Tegelbacken. The temporary arrangements mentioned in the preceding had ceased to exist on the 14th November, 1939, and the sewage from the Norrmalm drainage area was discharged after this date into the intercepting sewer in the Rosenbad Park, which sewer opens out into the pumping station at Karl XII's Square. There was thus a possibility to get samples from the drainage area in question. On the 15th February, 1940, we therefore collected 10 litres of sewage here.

The sediment precipitated from this sewage, which had been stored in the refrigerator-room until the 15th May, i. e. for *three months*, was prepared for inoculation into monkeys in the same way as in the first test (see above). The same as then, we recovered through the preparation two parts, one fraction A (= the clear liquid obtained through centrifugation) and a fraction B (= the sediment, suspended in physiologic salt solution), both shaken up with *ether* for achieving the least possible bacterial content — perfect freedom from bacteria was impossible to bring about. The virulence test thereupon commenced:

On the 29th May, 1940, are injected into *Macacus rhesus* V. T. 57 A of fraction A 25 cm³ peritoneally and 1 cm³ intrasciatically. The animal under observation until the 18th June without displaying any morbid disturbances and is now sacrificed, i. e. on the 20th day after inoculation. Strongly swollen lymph nodes in the mesenterium, inguines and axillae. Otherwise the internal organs are without any macroscopical changes. *Blood-culture*: no growth. The neuraxis presents histologically a fully *normal* aspect.

On the same day, or the 29th May, *Macacus rhesus* V. T. 57 B is given 60 cm³ of fraction B peritoneally and 1 cm³ intrasciatically. The animal dies on the following day of *peritonitis*. A new *Macacus rhesus* V. T. 57 B is

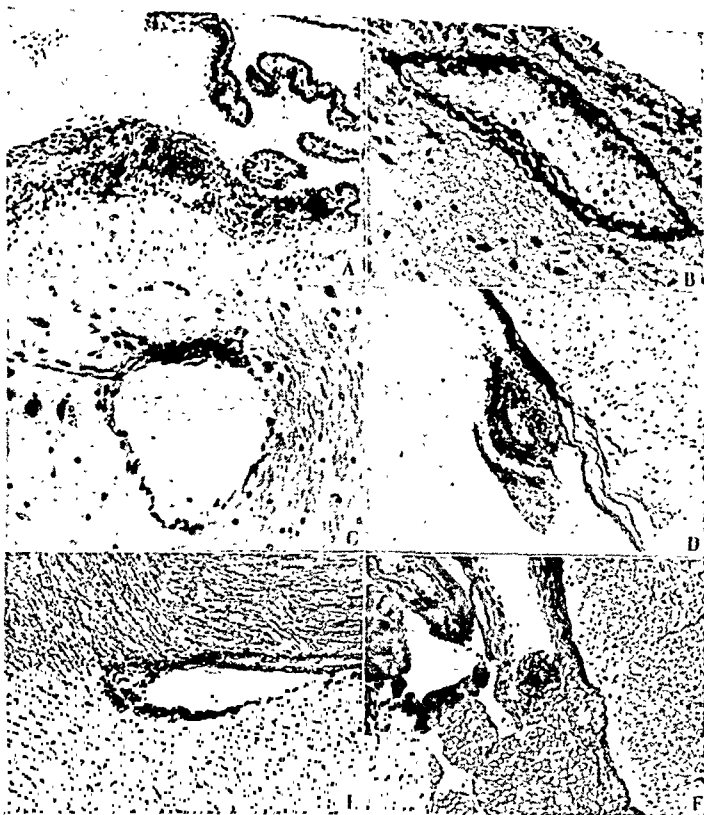


Fig. 5. *Macacus rhesus* V T 57 B with abortive poliomyelitis.

- A. Third ventricle with cellular infiltrations in the choroid plexus.
- B. Wall of the central part of one lateral ventricle, showing perivascular collar.
- C. Thalamus with the same lesion in the neighbourhood of the third ventricle.
- D. Medulla, showing perivascular meningitis.
- E. Medulla with perivascular collar.
- F. Lumbar spinal cord with perivascular meningitis.

infected with the same fraction (40 cm^3 peritoneally and 1 cm^3 intrasciatically). The monkey seems during the first days after inoculation intoxicated, but recovers soon completely and is kept under observation until the 18th June without showing any signs of paralysis. Sacrificed on that date, thus after 19 days. Mesenteric, inguinal and axillary lymph nodes voluminously swollen and red. Otherwise the internal organs look normal. *Blood-culture*: no growth. The microscopical examination reveals, as fig. 5 shows, widespread lesions of the type which we have seen to be present in the nervous system, when the abortive poliomyelitis occurs in the monkey (the patchy leptomeningitis on various levels of the brain, medulla and spinal cord, focal infiltrates in the choroid plexus, perivascular collars in the vicinity of the lateral ventricles, in the nervous tissue of the optic thalamus, pons and medulla; inflammatory process in spinal cord absent; its nerve cells apparently intact).

An attempt was made to transfer the abortive infection of monkey V. T. 57 B to a new test-animal. We selected for this purpose as transferring tissue the lymph nodes stored in glycerol in the cold — and this for the reason that in our previous passage-tests we had found that in monkeys with abortive poliomyelitis this material is mostly more infective than the nervous tissue. The result was, however, *negative*, as will be seen from the following experiment.

Macacus rhesus V. T. 57 C is given on the 6th July, 1940, cerebrally and peritoneally a suspension of the *mesenteric*, *inguinal*, *axillary* lymph nodes. The animal is kept under observation until the 6th August, i. e. for 31 days, without manifesting any clinical symptoms. The animal is sacrificed on that day. The microscopical appearance of the nervous system is entirely normal.

We have in the preceding been trying to draw attention to some of our observations regarding the occurrence of abortive poliomyelitis and its anatomical basis, and also accomplished fresh examples of such forms of the experimental disease, observed during the successive passages with the strain of poliomyelitis virus V. T. 51 isolated from Stockholm sewage in October, 1939. To judge from our experiences, the abortive poliomyelitis seems to make its appearance especially when the virulence of the causal factor for some reason or other is decreasing. We find this opportunity suitable to quote a particularly illustrative experimental example of such attenuation of the pathogenicity in a strain of poliomyelitis virus recovered from a specimen of feces originating from a typical case of poliomyelitis (case 4244/39, Karin V., treated at the Stockholm Isolation Hospital) and collected on the seventh day of the disease. The test material, when taken for inoculation, was stored in the refrigerator *under ether* for 50 days.

On the 24th November, 1939, *Macacus rhesus* 4244 is infected with 60 cm³ peritoneally and 0.5 cm³ intracerebrally of the clear liquid obtained in the ordinary manner — ether treatment and centrifugation of the fecal suspension. On the 11th December, or after 17 days, *typical* symptoms of *poliomyelitis*, which during the next day developed into full tetraplegia. Microscopically typical and severe *poliomyelitic* lesions in different levels of the neuraxis (see fig. 6).

On the 19th December, 1939, the glycerol-preserved neuraxis from this monkey is passaged in *Macacus rhesus* 4244 A by intracerebral and peritoneal injections. Typical symptoms of *poliomyelitis* on the 31st December, or after 12 days, produced, as the following histological examination disclosed, by *typical*, *intense* lesions.

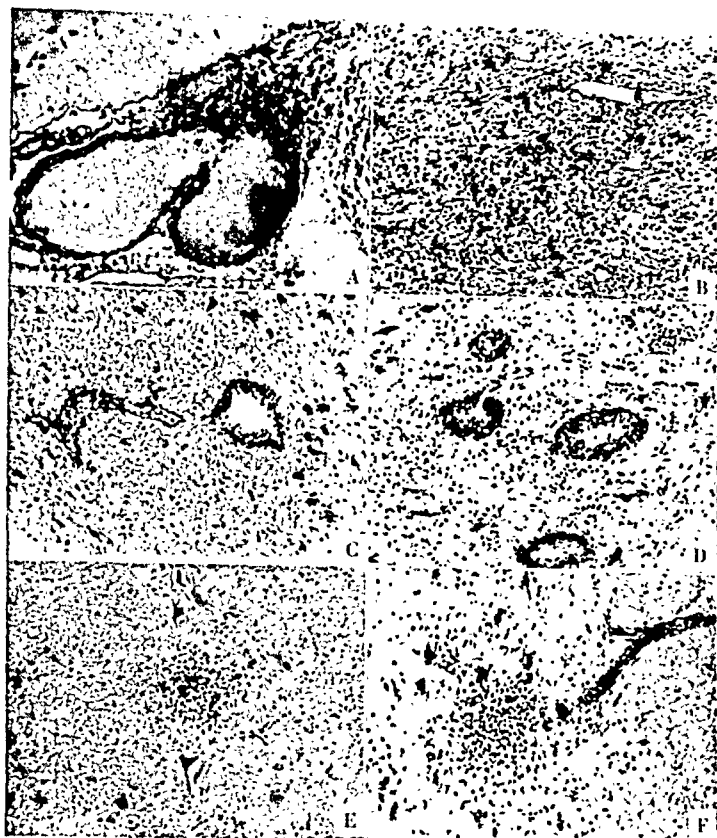


Fig. 6. *Macacus rhesus* 4244 with paralytic poliomyelitis.

- A. Frontal cerebral region with mighty perivascular meningitis in one of the sulci.
- B. Inoculation area (wall of central part of one lateral ventricle) showing a large glial infiltration in the corpus callosum.
- C. Hypothalamus with perivascular collars.
- D. Floor in fourth ventricle with perivascular collars.
- E. Cervical spinal cord. Note the focus of neuronophagia in the anterior horn.
- F. Lumbar spinal cord with perivascular collars and foci of neuronophagia in the grey matter.

In order to ascertain whether the stool specimen in question containing poliomyelitis virus was able to retain its virulence for any length of time when stored in the refrigerator ($+ 4^{\circ}\text{C}$) under ether, the following experiment was made:

On the 19th January, 1940, *Macacus rhesus* 4244 D is inoculated intracerebrally and peritoneally with approximately the same quantity of the fecal matter, after being stored under ether in the cold for 105 days and prepared as in the preceding stool-test. On the 24th January, or on the sixth day, the monkey shows tremor, and oculomotorius paralysis. These symptoms disappear soon, and on the 9th February, or 21 days after inoculation, the animal is sacrificed. In the histological examination the following lesions



Fig. 7. *Macacus rhesus* 4244 D with transitory-abortive poliomyelitis.

- A. Anterior part of one of the lateral ventricles with cellular infiltrations in the choroid plexus.
- B. Central part of one lateral ventricle with same lesions.
- C. Wall of the fourth ventricle showing perivascular collar.
- D. Medulla oblongata with same lesions.
- E. Cervical spinal cord showing perivascular collars in the boundary between the white and grey matter.
- F. Dorsal spinal cord with perivascular meningitis.

are found: Patchy leptomeningitis in various levels of the neuraxis (cerebral hemispheres, pons, cervical and dorsal region of the spinal cord, focal infiltrations in the choroid plexus of the lateral ventricles, numerous perivascular cuffings in the wall of the fourth ventricle and in the medullary tissue. Apart from the said meningitis the changes in the spinal cord are trifling. Here and there in the white and grey matter of the cervical region slight perivascular infiltrates are present, but no neuronal damage can be detected (see fig. 7).

The same test material which on the 50th day after its collection and storage in the refrigerator under ether had induced paralytic effect in the monkey, has after its continual preservation in a similar manner, altogether for 105 days, been able to give rise by

inoculation to an experimental disease of a transitory-abortion character. The lesions of the central nervous system had in this case the same localisation and the same appearance as those which we not rarely have observed inter alia in passaging typical strains of poliomyelitis virus to other monkeys. In this instance the lesions were especially pronounced in the floor of the fourth ventricle and in the medulla. If we add to this, that the changes seem to have been set up by a causative agent of a virus nature *resistant to ether*, there should not be any doubt that we have succeeded once more in recovering the poliomyelitis virus from the same test material, though with a lower degree of pathogenicity. A passage accomplished with the neuraxis from the said monkey might *possibly* have given further evidence of the specific nature of the lesions. We say »possibly», for in consideration of our earlier experiences we expected to have only very small prospects in producing the typical paralytic disease with that passage material. For we have only in two cases of abortive poliomyelitis in monkeys (of *meningo-cerebral* type) noticed a tendency of the virus to increase its pathogenicity in such measure that the presence of pontino-spinal lesions with neuronophagia in the grey matter of the spinal cord could be recognised in the passages.¹ But also in these passages the infection established developed without clinical symptoms. In the rare cases in which the experimental abortive disease gives a positive result in the passages, it is more usual for the inflammatory process of the neuraxis to present a similar appearance and localisation as in the primarily inoculated animal. In an ensuing paper we shall deal more thoroughly with the question concerning the abortive, experimental poliomyelitis, and the criteria for its diagnosis.²

¹ Loc. cit.

² Recently, also Sabin and Ward in «The Journal of Experimental Medicine» (Vol. 73, No 6, June, 1941) related their observations of «non paralytic» poliomyelitis in monkeys after inoculation with human or first passage virus — anatomically characterized by an outfall or destruction of the neurons in the grey matter of the spinal cord, through the presence of degenerative reactions in the nerve roots, together with more or less pronounced infiltrative lesions in the different levels of the neuraxis. They established, similarly to us, the great difficulties in attempting to pass the abortive infection to other monkeys (of 14 cases only two positive passages with the development of typical paralytic poliomyelitis). We can in this connexion not omit to express our surprise at the nonchalance with which the American investigators try to make out that the monkeys used by us had been affected with a *spontaneous* infection, maintaining that the vascular lesions observed by us in the neuraxis of the monkeys inoculated with human virus or with passage-virus (derived from

The interest attaches in the first instance to the striking similarity of the lesions present in the central nervous system of monkey 4244 D, to those revealed in *Macacus rhesus* V. T. 57 B, inoculated with the specimen of sewage collected on the 15th February, 1940, or three months after the cessation of the poliomyelitis epidemic in the capital. The comparison can be carried still further. With test material from the same vehicle, sewage from the Norrmalm drainage area, but obtained on the 11th October, or at the height of the epidemic, we had succeeded in producing in the monkey the typical paralytic disease with intense characteristic lesions. Even in the serial passages accomplished with this strain we have observed the abortive infection showing histological findings prevailing in the upper regions of the neuraxis (monkey V. T. 51 B, see above), in other words, the same clinical type and quite the same anatomical substratum as in the »stool-monkey» 4244 D and the »sewage-monkey» V. T. 57 B. We believe, therefore, to have strong reasons to draw the conclusion that the presence of the poliomyelitic virus in the Stockholm sewage has been demonstrated also in the second test, i. e. three months after the epidemic had ended. However, the power of infection of the strain recovered in this test appears to have been decreasing and become so attenuated that our attempts to transfer the infection to other monkeys failed.

Issuing from the experimental observations related in the preceding, it seemed as a matter of course of importance in one respect or the other to follow farther the fate of the poliomyelitis virus in

typical strains) and showing the abortive or transitory poliomyelitis had in reality been the histological base of such an infectious process — and this in spite of our definite and well-founded assurance to the contrary, i. e. that we have been able to exclude the occurrence of a spontaneous disease in our test-animals (see International Bulletin, Vol. A 40: Infantile Paralysis, Note 2, p. 171; a regrettable misprint — »inoculated» should be read »uninoculated» — appears to us hardly to constitute a satisfactory ground for their hastily discriminating our findings from their own, especially so since in our earlier note in *Acta Medica Scandinavica*, 1933, p. 634, in which we dealt with the elimination of the virus through intestine, we also ventilated the same question with the use of the term »singes non inoculés»).

Even Bodian and Hope have quite recently (see Bull. of John Hopkins Hospital, Vol. 69, No 2, August 1941) been able to establish the occurrence of a »non-paralytic» type of experimental poliomyelitis. These investigators have, similarly to ourselves — yet without mentioning the previously made Swedish observations — observed that the poliomyelitic process induced in the monkeys under certain conditions may be limited to the upper regions of the neuraxis, and thus arrested before involving the spinal cord. One must, in other words, reckon with an *encephalitic* form of the experimental disease.

Stockholm sewage. In order to illuminate this question we therefore proceeded to a third sewage-test. Ten litres of sewage were on the 18th August, 1940, collected at the pumping station at Karl XII's Square, i. e., at the same site as in the second test, and at a moment when, after a lapse of *nine months* since the last case of poliomyelitis had been diagnosed in the capital. The test was carried out in the same way as before.

From fraction A (the clear liquid recovered by centrifugation) *Macacus rhesus* V. T. 59 A is given 40 cm³ peritoneally and 1 cm³ intrasciatically on the 31st October, 1940 (after the sediment had been kept in cold storage for about 2 months). The animal was kept under observation until the 28th November, i. e. 28 days, without displaying any paralytical symptoms, for which reason it was killed for histological examination. Everywhere in the neuraxis a *normal appearance*.

Macacus rhesus V. T. 59 B infected on the same day, the 31st October, 1940, with 20 cm³ of fraction B (the sediment suspended in physiologic saline solution) peritoneally and 1 cm³ intrasciatically. After 21 days' observation, during which the monkey seemed to be in good health, it is sacrificed and in the microscopic examination of the neuraxis *nothing abnormal* could be detected.

This third and last test thus gave an entirely *negative* result. The poliomyelitis virus seems, in other words, to have disappeared from the sewage derived from the Norrmalm drainage area — at least in a degree of virulence disclosable by the ordinary method.

D. *Review and discussion.*

The establishment of the presence of poliomyelitis virus in Stockholm sewage gives us cause for several comments of a practical and theoretical nature. In order to facilitate this discussion we have deemed it suitable to summarize the results of the investigations in the following survey (table 2).

As is seen from the preceding account, there has been isolated on the first test occasion, 11th October, 1939, i. e. in the height of the poliomyelitis epidemic prevailing in Stockholm, a strain of poliomyelitis virus, giving rise to the typical experimental disease (with paralytic symptoms and the characteristic lesions in brain and spinal cord), and which could be transmitted in serial passages.

Table 2.

Date of sampling of sewage	Cronological relation of tests to the Stockholm epidemic	Storage period of sediment (in refrigerator) before examination	Result of inoculation	Clinical type of experimental disease	Pathologico-anatomical lesions
11/10 39	During epidemic	2 months	<i>positive</i>	Manifest	Cerebrospinal type
15/2 40	3 months after cessation of epidemic	3 months	<i>positive</i>	Abortive	Meningo-cerebro-pontino-medullary type
18/8 40	9 months after cessation of epidemic.	2 months	negative	—	—

But in addition to this we have seen that this strain has also given rise to *abortive* forms of disease («non paralytic» according to Sabin and Ward's nomenclature) which fact seems to be due to a decrease in the virulence of the strain — a phenomenon which we have noticed repeatedly in regard to our *typical* strains of poliomyelitis virus isolated since the summer of 1936, and which we have placed on a level with the attenuation of the infective power of the *rabies virus* observed by Pasteur in his classical experiments on monkeys. We have in the preceding also quoted an example of how a poliomyelitic strain at its first isolation from a stool-specimen manifested a relatively high degree of pathogenicity, but at the second recovery from the same test-material after the continued storage under ether had been so reduced in its activity that it was merely able to induce an abortive infection (revealable by the histological examination).

In the light of the experimental observations, quoted above, we consider that we have sufficiently established — if also only in an indirect manner — that Stockholm sewage even at the second test, undertaken three months after the cessation of the epidemic, harboured the virus of poliomyelitis. But during the time elapsed since the moment of the first test the virulence of this agent seems to have been so reduced that its effect on the monkey was confined to the occurrence of the abortive type of infection with lesions limited to the upper regions of the neuraxis.

One asks of course: Has it been a lucky chance that brought about our success in demonstrating the presence of poliomyelitis virus in Stockholm sewage, or have we with this finding illuminated a regularly recurring phenomenon? To judge from our own investigations and those of the New Haven investigators one might be entitled to conclude that it is the latter alternative which corresponds to the reality. We ourselves had on two different test occasions, with 4 months' intervals, been able to demonstrate the virus content of sewage. When the American experimentors during epidemics in two localities were in search of the virus in sewage they found it at two different sites of the sewers selected for the sampling, and disclosed it there on four different occasions (once at *Charlestone* and three times at *Detroit*). On examining a specimen of sewage from a third place (*Buffalo*), where an epidemic was prevailing, collected at such a point of the city sewers that it represented a more or less restricted area, «island community» — with a population of about 750, and within which three cases of poliomyelitis had occurred — the monkey inoculated displayed after 16 days' incubation a clinical picture of poliomyelitis, which in the histological examination proved to be due to typical poliomyelitic lesions. Repeated attempts to transfer this disease to other monkeys failed, however, for which reason, even if with a certain amount of hesitation — especially in one of their first publications — this result of inoculation was interpreted as negative.¹

The positive test results registered at *Charlestone* and *Detroit* have this in common that the samples of sewage were taken in *immediate conjunction with, or in close vicinity to isolation hospitals where poliomyelitis patients were admitted*. For that reason it was

¹ According to our by no means small experience this judgment seems to bear the impress of far too great circumspection. Even typical strains of virus isolated from human poliomyelitic material may possess such a low virulence that they could not, or only with great difficulty, be passed on to subsequent monkeys. Here is an exemplification of this phenomenon. Of 8 typical strains of virus (belonging to our Jämtland material from the epidemic of 1938) isolated from fatal cases of poliomyelitis, the passage failed twice. During the epidemic of infantile paralysis in Stockholm in the summer and autumn of 1939, we recovered 7 typical strains with the use of stools derived from paralytic cases of poliomyelitis as inoculation material. With *two* of these strains we failed to reproduce the infection in new monkeys. As the clinical symptoms and the changes in the neuraxis of these animals were fully characteristic in the said 4 cases, and as no other infectious agent than poliomyelitis virus is known to possess these properties (spontaneous infection being a very rare phenomenon in the monkey, it might without any further ado be excluded) we did not hesitate to consider also these inoculation results as positive.

possible that these individuals constituted the source for the infectious agent isolated from the specimens of sewage collected — which also the authors for special reasons reckoned with. Whether the same has been the case with the samples of sewage obtained and pooled from the «island community», cannot with certainty be gathered from the account published.

We have been desirous of pointing out this because these experimental observations — at least in so far as those made at Charleston and Detroit are concerned — in epidemiological respects differ essentially from the Stockholm finding. The samples of sewage carrying poliomyelitis virus taken during the Stockholm epidemic respectively after its cessation, were derived from a drainage area which *had no communication with the sewer from the isolation hospital*. In a later paper written after our first note, Paul and Trask¹, however, mentioned briefly a fresh experimental observation, made during a poliomyelitis epidemic raging in New York City in the summer of 1940, and which to some extent seems to correspond to the Swedish one. On testing a specimen of sewage collected from a large sewer of the city which very likely did not directly emanate from any ward where poliomyelitis patients were under treatment («not in the vicinity of an isolation hospital, although cases of poliomyelitis were present within the areas this sewer drained»), the poliomyelitis virus could be isolated also from this sewage.

From the observations now made in several places it seems to be obvious that it is relatively easy, while an epidemic of infantile paralysis is prevalent in a district, to isolate the agent of the disease from its sewage. Of a certainty the experience will, when there has been time for investigations on a larger scale, be the one indicated here. It seems considerably easier to establish the presence of poliomyelitis virus in sewage than to recover the ordinary pathogenic intestinal bacteria from the same medium. Upon what the cause of this difference depends, we are as yet in ignorance. But it is clear that the virus of poliomyelitis must exist in the vehicle here concerned in very large quantities, inasmuch as one succeeds in revealing its appearance by way of the usual experimental test — as we have pointed out in the preceding about 3 million doses infective for the monkey should have passed through the Norrmalm sewer during

¹ Paul and Trask, «The virus of poliomyelitis in stools and sewage. Journ. of Amer. Med. Ass., 1941, 116, 493.

twenty-four hours when the first specimen of sewage was collected. We have in the preceding discussed different possibilities as an explication for the massive presence of poliomyelitis virus in sewage, and found it most plausible that a multiplication of the same has taken place. How one is to think of the conditions for this multiplication, we shall revert to in the ensuing.

By establishing in various quarters that sewage may harbour poliomyelitis virus, the similarity in principle between infantile paralysis and certain bacterial diseases of the intestines, such as, by way of example, typhoid, paratyphoid, dysentery and cholera, has become still more striking. The same as in the said infectious diseases, the causal factor in poliomyelitis can via the stools be discharged into the sewer system of the district, and thence carried farther to water-ways with which human beings are in more or less close contact. The conception of poliomyelitis as an *alimentary infection* has with these new gains of poliomyelitis research found further and powerful support — an opinion which by one of us (Kling) has been vindicated since 1928, based upon clinical, epidemiological and experimental observations.

In connexion with his studies, carried out at the request of the Hygienic Section of the League of Nations, of the epidemics of infantile paralysis in Saxony and Roumania during the year 1927, combined with a comparative retrospective critical examination of the previous severe epidemics in Sweden during the years 1905, 1911, 1912, and 1913, Kling effected a revision of the experimental results reported by Pettersson, Kling and Wernstedt¹, as well as by Levaditi and Kling² in regard to the presence of poliomyelitis virus in the human *pharyngeal secretions* and in the *intestinal contents*. In this revision, based inter alia upon renewed examination of the old histopathological material, which is still in existence at our institution,³ all doubtful results of inoculation (experimental animals with so-called »degenerative» changes) were excluded and only such indubitable result were counted, as had become apparent from the fact that the experimental animals had displayed *typical symptoms of poliomyelitis* and that the histological examination had disclosed *typical lesions* (the presence of the ordinary perivascular and focal cellu-

¹ Kling, Pettersson and Wernstedt, »Investigations on Epidemic infantile paralysis». Rep. f. State Med. Inst. of Sweden to the International Congress of Hygiene and Demography, Washington 1912, Nordiska Bokhandeln, Stockholm.

² Kling et Levaditi, Annales Inst. Pasteur, 1913, 27.

³ See Kling, Bull. Office Int. d'Hyg. publ. 1928, 22, 1779 and Act. Soc. Medic. Suecanae, 1929, 55 (with all details of the investigation).

lar infiltrations in the grey matter of the spinal cord, as well as the characteristic neuronophagia) — in some cases verified by positive passages. From the summary made subsequently it was seen that the poliomyelitis virus had been detected 2—3 times as often in the intestinal content (8 positive tests out of 68 cases examined) as in pharyngeal secretion (6 positive tests out of 110 cases examined). It was *inter alia* by reason of this critical examination of the original experimental material that Kling drew the conclusion that the entire digestive tract (including the pharynx) represents the locality where the agent of the disease primarily attacks the organism, and that the intestine constitutes the most important organ of excretion. He considered, therefore, that he had reason to fit poliomyelitis into the group of intestinal diseases.

It has seemed to us necessary once more to emphasize the deletion made by Kling in 1928 of all uncertain cases from the results of experiments reported in 1911—1913, which sundry investigators into poliomyelitis in the U. S. A. — yet not all — seem to be ignorant of. This holds good, *inter alia*, of Sabin and Ward, to judge from their recently published work.¹ These authors have during the year 1940 undertaken — with a rational exploitation of a limited material derived from necropsies and with the use of those methods which are now available — to try by new experiments to arrive at full clarity of the distribution of the poliomyelitis virus within the human organism. By testing the specific activity of various organs it was possible to demonstrate the presence of virus, apart from the neuraxis, also on the pharyngeal mucosa, in the walls of the digestive tract at different points and in the intestinal content (in all cases examined). On the contrary, the tests for the causal factor in the nasal mucosa, in the olfactory bulbs and in the anterior perforated substance gave negative results. The pattern of the distribution of the virus in human poliomyelitis so established thus indicates, according to the opinion of these experimentors, the alimentary tract as portal of entry. The *gastro-enteric* theory had with these findings obtained important support. That Sabin and Ward have very incompletely penetrated the work of their predecessors, is apparent in their comments on the previous Swedish results of research. For they state on page 790: «However, the clues contained in the work of Kling, Wernstedt and Pettersson were not pursued and remained dormant for a quarter of a century chiefly because in their subsequent work on intestinal contents and naso-pharyngeal washings from patients and contacts it became apparent that they often employed criteria for the presence of virus which were found not to be acceptable.» The same lack of knowledge of the experimental details they also manifest in their judgment of Kling, Olin and Gard's find of poliomyelitis virus in certain lymph nodes² — a find of great importance for the question concerning the pathogenesis of poliomyelitis, i. e. the spread of the virus from the portal of entry — the walls of the digestive tract — to the site of predilection, the grey matter of the

¹ Sabin and Ward, «The Natural History of Human Poliomyelitis», *Journal of Exp. Med.* 1941, 73, 771.

² Kling, Olin and Gard, *C. R. Séances Soc. Biol.*, 1938, 129, 451.

spinal cord. We shall revert explicitly to this question in another connexion, but wish nevertheless already here to emphasize that the five positive results with lymph nodes, which Sabin and Ward are commenting, were based upon observations of experimental poliomyelitis with *typical symptoms* and *typical lesions*, and which could be transmitted in serial passages. We are, therefore, convinced that since Sabin and Ward should have acquired further experience in this respect, they will, similarly with us, be able to demonstrate the virulence of the lymph nodes in question (whether as an expression for centripetal dissemination of virus from the portals of entry via the lymphatic paths or as an expression for a generalised lymph node infection, we do not wish to say).

The experimental investigations carried out by Kling, Levaditi and Lépine in co-operation with Hornus¹ during the years 1929—1934, establishing that it is possible via the digestive tract to infect *Macacus cynomolgus* with poliomyelitis (by administering a virulent suspension of spinal cord, by artificially contaminated food, such as water, potatoes, bananas, butter) have been confirmed through recent experiments by Trask, Vignac and Paul², by Burnet, Jackson and Robertson³ as well as by Howe and Bodian⁴.

That it took more than a quarter of a century before the *gastro-intestinal* theory was able to penetrate, and has now begun to be accepted also by leading experimenters in the U. S. A., is very likely, in our opinion, due not so much to certain deficiencies in the earliest Swedish researches — as Sabin and Ward are trying to make it appear probable — but rather to the circumstance that one of the foremost poliomyelitis investigators, Simon Flexner, ever since the beginning of the experimental studies on infantile paralysis, has so one-sidedly maintained the rôle of the nasal mucosa as the portal of entry for the infection, and that he has obtained so many adepts both in his own country and elsewhere. As late as the year 1936 he relates in his publication «Respiratory versus gastro-intestinal infection in poliomyelitis» about new experiments carried out by him, which were directly induced through the investigations by Kling, Levaditi and Lépine, mentioned here before, and which seemed to him to supply further proofs for his «respiratory» theory, while in regard to the gastro-intestinal hypothesis he expresses himself in the following manner: »The gut is not a favourable locus for the virus. Under the circumstances it is not, therefore, among other things probable, as Kling and Levaditi would have it, that virus escaping from the intestine may contaminate potable water supplies, be thus widely distributed, and result in water-borne epidemics of poliomye-

¹ Kling, Levaditi et Lépine, Bull. de l'Acad. de Méd., 1929, 102, 158.

Kling Levaditi et Lépine, (en collaboration avec M. T. Ekblom), Bull. de l'Acad. de Méd., 1931, 106, 245.

Levaditi, Kling et Hornus, C. R. Séances, Soc. Biol., 1933, 112, 43.

Kling, Levaditi et Hornus, Bull. de l'Acad. de Méd., 1934, 111, 70.

² Trask, Vignac and Paul, Journ. Amer. Med. Ass., 1938, 111, 6.

³ Burnet, Jackson and Robertson, Austr. Journ. Exp. Biol. and Med. Sc., 1939, 17, 375.

⁴ Howe and Bodian, Proc. Soc. Exp. Biol. and Med., 1940, 43, 718.

litis.¹ It was not to take many years after these words had been pronounced before — through American and Swedish researches — it was made clear, that sewage during epidemics of poliomyelitis can harbour the etiologic agent, a medium whence water used for drinking purposes, can easily be contaminated.

From our tests with Stockholm sewage it has been made manifest (see table 2) that poliomyelitis virus under experimental conditions can retain its virulence for a period of at least 2—3 months at a temperature of $+4^{\circ}\text{C}$. This observation seems to us to present a no small epidemiological and hygienic interest.

According to information gathered from expert quarters the mean temperature for Stockholm sewage varies during the spring, summer and autumn months (May—September) between 13 and 23°C , during the winter months (October—April) it keeps in the daytime at about $+10^{\circ}\text{C}$ and during the night at between $+6$ to 7°C . We know through experimental observations made by Kling, Levaditi and Lépine² that poliomyelitis virus keeps alive in drinking water from public supplies at least 114 days at laboratory temperature. We have, therefore, every reason to assume that this infectious agent both during its stay in the sewer and after getting into the recipient and its effluences of different kinds can retain its vitality and its pathogenicity for some considerable time — if the sewage has not undergone the necessary disinfection before that time. Unfortunately, it is not customary for such hygienic measures to be adopted. In many places in our rural districts and in our smaller urban communities the sewage is allowed without any further ado to empty into the recipient on the so-called perpendicular system — our country is certainly not alone in offending in this way. Hence the serious consequence that during those periods when infantile paralysis is epidemical, we have to reckon with *the sewage as an important source of infection, from which the disease can spread over vast areas*.

In the work quoted in the preceding Kling set forth epidemiological observations from the three countries mentioned, showing that the epidemic outbreaks of poliomyelitis without exception occur in the vicinity of water systems (rivers, brooks, lakes, sea) and that in countries such as Roumania and Sweden, where from a demo-

¹ Flexner, Journ. Exp. Med., 1936, 63, 224.

² Loc. cit.

graphic point of view one can draw a distinct line between rural and urban settlement, the country people are more attacked by the disease than the urban population — a phenomenon which was placed in connexion with the poorer water hygiene existing in the rural areas. Kling concluded that »sans eau aucune formation de foyers poliomyélitiques» and »que l'eau constitue un véhicule important de germe poliomyélique et qu'elle joue un rôle de premier ordre pour la transmission de la maladie». Infantile paralysis is, in other words, according to this conception to be brought into the group of infectious diseases which have their origin in polluted water and which the Anglo-Saxons term »water-borne diseases», and the French »maladies hydriques». It goes without saying, that this water-theory through the discoveries now made in respect of the presence of the poliomyelitis virus in sewage, has gained very strong support, which also seems to be Levaditi's opinion.¹

Poliomyelitis research has now at long last — though it has taken more than three decades — got so far, that we may say that we have now a good knowledge of two links in the mechanism of transmission, viz. the human individuals suffering from poliomyelitis or »inapparently» infected persons, from whom the virus, in the first instance via the stools is eliminated; we know also the vehicle where the infectious agent, while the epidemic is going on and for some time after its end, dwells, i. e. the sewage. It remains now for this research to try to clear up more particularly also the other links in the chain of transmission. We are already able analogously to draw some conclusions. The mode of transmission of the bacterial intestinal diseases lead our thoughts to water-supplies and to infected food polluted by the virus of poliomyelitis. Our institution has been trying for several years with the same starting points — though not so fixed and sure as with our present knowledge — to illuminate the rôle of the said vehicles as virus carriers. As regards the importance of the water as a carrier, certain preliminary results have already been published^{2, 3}, and a detailed account of the same will be supplied at the earliest possible opportunity. Even in so far as concerns the possibility of food being able to play the same part, there was at our institution during the year 1939

¹ See Bull. Acad. Médecine, 1940, 123, 337.

² C. Kling, »In Search of Poliomyelitis Virus in Drinking Water, Loc. cit. and Nordisk Medicin 1941, 25, 1954.

³ R. Spaak, Ibidem, 25, 1952.

made an epidemiological and experimental observation of the greatest interest, viz. regarding butter.¹ This observation, which constitutes very instructive evidence of the rôle of sewage for the dissemination of poliomyelitis virus, will likewise be submitted in *detail*.

The prophylaxis of infantile paralysis has as a matter of course through the experimental progress of late years assumed a new and more hopeful aspect. The guardians of hygiene have in regard to this prophylaxis still quite a good deal of work to do, but there is no reason to enter here into details. Nevertheless, we wish to state, that recent observations from our own country have been communicated, showing that persons busy with pudrette-work, or children whose fathers have been working with sewage installations, have been attacked by poliomyelitis. It is, of course, quite natural — even if not experimentally established — to try to search for the source of infection of these cases of sickness in sewage contaminated with poliomyelitis virus.

¹ N. O. Heinertz, *Ibidem*, 25, 1953.

From the State Bacteriological Institute, Stockholm.

Sewage as a carrier and disseminator of Poliomyelitis Virus.

By

C. KLING, G. OLIN, J. FÅHRAEUS and G. NORLIN.

(Submitted for publication April 15, 1942).

Part II.

Studies on the Conditions of Life of Poliomyelitis Virus outside the Human Organism.

From the preceding it seems to be obvious that the presence of the poliomyelitis virus during an epidemic can without any great difficulty be demonstrated in sewage — an observation which in our opinion indicates a massive, if also temporary, occurrence of this agent in the said medium. Our epidemiological observations, made in connexion with the establishment of the virus content of Stockholm sewage in the autumn of 1939, gave us cause to assume that the virus, after leaving the human organism and passing into the sewage, afterwards in some way or other has undergone a multiplication. But this process of life can only be realised by the presence of an organism, in which this infectious agent, being of an ultra virus nature, finds good conditions for its growth. Where is one now to look for this vector, and of what kind is it? Does it live *above* the surface of the sewage or is it perhaps to be found *within* this vehicle itself?

When Levaditi became acquainted with our find of poliomyelitis virus in Stockholm sewage, and commented upon it in Académie de Médecine¹, he put forward the suggestion that there must be

¹ Loc. citat.

some »animal vecteur» as an intervening party and queried the possibility of sewer rats being able to play such a rôle. This idea may, of course, appear plausible if one considers the extraordinary abundance of rats prevailing in certain parts of the Paris sewers. One of the characteristics of the main sewers of this metropolis is, as is known, that they represent an open system, on the banks of which the rats find excellent conditions of existence. We proceeded at once to an examination of this idea. Our experts rejected it without hesitation — at least in so far as the Stockholm sewer system is concerned. Within the drainage areas of the city — i. e. also where we collected the specimen of sewage harbouring the poliomyelitis virus — the sewers are composed of a system of closed drains. Here the rat has certainly no prospects of existence, still less of propagating.

We investigated thereafter another possibility. May there be some insect which has its existence as *imago* above the surface of the sewage, and whose other links in the cycle of development proceed within this medium? One of our foremost entomologists (Professor Lundblad) was asked on this subject. We received the answer that the idea of a vector of this kind was very little probable. These arthropodes certainly very unwillingly, if ever, look for such a vehicle as sewage when they are about to lay their eggs.

For those reasons we were obliged to devote our attention to the *sewage* itself. For here micro-organisms of all kinds abound — unfortunately far too many, one is tempted to say, so that in the search for and capture of the hypothetical intermediary host one can have any hopes of gaining speedy results.

For about one year we have been busy on these investigations. Even if the problem in question to start with seemed to have been simplified to some extent, inasmuch as the search aimed at certain definite vehicles, viz. sewage, as well as those water-supplies of different kinds which may be polluted by such a fluid, it was yet soon clear to us that, as has just been suggested, we were nevertheless faced by a difficult task. The organisms which have their existence in these vehicles and whose character as vectors had to be considered, are in fact extremely numerous and represented by both animal and vegetable beings (zoo- and phytoplankton). We were, therefore, soon forced, as we shall see in the ensuing, to pursue a more rational line.

Our researches in this domain are as yet only in the very beginning, and we are only able here to give a few preliminary results achieved. On studying this problem one must, of course, reckon with experiments on animals. Under the pressure of the prevailing international situation our possibilities to procure the necessary test-animals — monkeys — are extremely limited. With the purpose to try to interest experimenters, who are better situated than we in this respect, for searching for the vector of poliomyelitis, we take the liberty to sketch here briefly the working project which we are trying to pursue at present.

The vector of poliomyelitis — if now such an one really exists — should, we reasoned, be most easily found in the vehicle by means of which the virus, from what we know now, mostly leaves the infected individual. In the fecal matter the different kinds of accompanying micro-organisms ought to be less numerous than in the medium that is suspected as a source of infection, i. e. the water-supply carrying the hypothetic vector, as also in the recipient, where the former might enter with the poliomyelitic stools — the sewage — and this in all probability as the result of the destructive action of the acid gastric juices. It seemed to us, therefore, indicated to begin with a comparative morphological study of those micro-organisms that exist in the said media. Perhaps we would through such a study find something common to these, which might give us a clue to further proceeding in these researches.

At first we tried by direct examination — in the darkground-microscope — to discover something distinctive for the infected media but we were soon convinced, that this was no practicable way, particularly not in regard to intestinal contents. It became instead clear, that the best procedure for our purpose ought to be the culture method — this, of course, on the presumable condition that the assumed vector was cultivable. As we first of all had some one of the water protozoa in our minds, it was a matter to select a technique which would be serviceable for the cultivation of these organisms. As usable for these researches we found the method described by Glaser and Coria¹ in 1935, and intended specially for the cultivation of protozoa in a pure condition.

¹ Glaser and Coria: »The culture and reactions of purified protozoa». American Journ. of Hygiene 1935, 21, 111.

We therefore made use of Glaser and Coria's medium, according to the instructions containing horse-blood serum and infusion on hay (timothy-hay) in certain proportions, with *well-water* as a *diluent*, and with an admixture of a minimal quantity of *yeast-extract*, as a stimulant for the growth of protozoa. As to the quantitative composition of the medium, we refer to the authors' publication. Some minor modifications regarding the diluent and admixture of yeast have, however, been made by us.

Instead of well-water we have been using filtered and sterilized lake-water (from Lake Maelar).

In the preparation of the growth-promoting yeast component we proceeded in the following manner: 100 g baker's yeast, stirred in a small quantity of distilled water, is ground intensively in a largish mortar (during 1 hour), by which means a finely distributed suspension is obtained. Dilution of the suspension by means of distilled water to 1000 cm³. Strong centrifugation for ½ hour. The faintly opalescent supernatant yeast suspension is pipetted off and is now ready for use (for our purpose filtration unnecessary and unsuitable, as is also sterilisation, which according to Glaser's and Coria's experience destroys some or all the stimulating factors).

If the protozoa only sparsely occur in the test-material, it is naturally of advantage to issue from as large quantities of the same as possible. We have, therefore, for our cultures used large aquarium vessels, which easily hold the different components — altogether a quantity of 3325 cm³. For covering the aquaria have been used as lids so-called photographic bowls, which prevent contamination from the air and permit the convenient insufflation of air into the culture medium under the ordinary precautions for sterility.¹

In the cultivation of *sewage* and *water* samples 3000 cm³ have been taken as starting material. An admixture of 300 cm³ of the medium (Glaser's and Coria's «final medium») as well as 25 cm³ of the yeast suspension.

When it has been a case of cultivating *fecal* matter, the procedure has been this: Stools from the respective individuals have as a rule been obtained through a clyster (with sterilized city tap-water). If the fecal suspension is just about the right thickness, which is estimated by a comparison with a 5 % standardised fecal suspension, it is used as such; if it is too thick, dilution with sterile water is necessary. 300 cm³ of the fecal suspension (containing about 15 g of the stool) is mixed with 2700 cm³ of sterilized lake-water, 300 cm³ medium and 25 cm³ yeast suspension.

Adjustment of the reaction of the culture medium to pH 7.2—7.4.

The cultivation must proceed at room temperature (it has varied between 16—24° C) and in semi-darkness. Airing of the culture every day for about 8 hours.

Examination of the culture in the *dark-ground-microscope* after 8 respectively 14 days. If no protozoa are met with after the last-mentioned

¹ For airing we have made use of electrical air pumps connected with a sterile system of tubes, consisting alternately of metal and rubber, and terminating in a finely protracted glass tube, which dips into the liquid.

period, passage of cultures (transfer from the primary culture of 300 cm³ in a fresh medium of the same quantity and the same composition as the original one).

Repeated examinations after 8 respectively 14 days. Definite reading. When such has been considered desirable, the »positive» cultures have been transferred to sub-cultures for further study of the morphology of the organisms observed and for experimental purposes.

In order to convince ourselves that no contamination by air has occurred, and that no protozoa have developed out of the yeast suspension, every time an initial culture was prepared or a subsequent transfer took place, one or more *control* aquaria were established, containing lake-water, medium and yeast suspension in the same quantities and proportions as the cultures inoculated.

From this angle of view, we have ever since the summer of 1940 examined a large number of stools¹ from typical and abortive cases of *poliomyelitis* (over 80). A few months earlier, in conjunction with the virulence tests of the Stockholm sewage, we began to search for the vector in this medium and likewise in drinking water which by respective medical men had been suspected as sources for cases of poliomyelitis. The Stockholm sewage has in this respect been tested on three separate occasions (11th October, 1939, 15th February, 1940 and 18th August, 1940). The samples of water tested amount at the moment of writing to nearly 40, covering different kinds of water — from wells, from springs polluted by surface water, from brooks, rivers, seas, lakes. Besides, we have for purposes of control tested drinking water obtained through filtration and chlorination of lake-water or derived from ground-water wells. For judging the finds in poliomyelitic stools it is, of course, necessary to acquire a knowledge of the fauna and flora in samples of stools of another kind — a control material that must be sufficiently extensive and comprehensive. We have also begun to procure such. So far, we have had occasion to investigate cultures from 36 samples of stools derived from individuals with different diseases (scarlet-fever — in a preponderating number — some odd cases of herpes zoster, epidemic cerebrospinal meningitis and encephalitis) as well

¹ During the summer and autumn of 1940 these specimens were chiefly obtained from the Isolation Hospitals at Linköping, Söderköping, Falun, Borlänge and Varberg; during the poliomyelitis epidemic of 1941 the stools were obtained from the Isolation Hospitals at Stockholm and Uppsala.

We avail ourselves of this opportunity to express to the Head and the Staff of these hospitals our warmest gratitude.

Table 1.

II. Human stools			
I. Samples of water (wells, springs, brooks, rivulets, rivers, lakes, sea)	A. Poliomyelitis 85 samples tested	B. Other infections (scarlet-fever, zoster, epid. cerebrospinal meningitis, encephalitis) 36 samples tested	C. Healthy individuals 10 samples tested
33 samples tested Class MASTIGOPHORA Order <i>Protopomonadina</i> Genus <u>Bodo</u> <u>Monas</u> Order <i>Polymastigina</i> Genus <i>Trepomonas</i> Hexamitus Class RHIZOPODA Order <i>Amoebina</i> Genus <u>Amoeba</u> Order <i>Heliozoa</i> Different genera Class CILIATA Order <i>Holotricha</i> Genus <i>Paramaecium</i> Balantidium Cyclidium Glaucoma Coleps Order <i>Oligotricha</i> Genus <i>Pleurotricha</i> Order <i>Peritricha</i> Genus <i>Vorticella</i>	Class MASTIGOPHORA Order <i>Protopomonadina</i> Genus <u>Bodo</u> <u>Monas</u> Class RHIZOPODA Order <i>Amoebina</i> Genus <u>Amoeba</u>	Class MASTIGOPHORA Order <i>Protopomonadina</i> Genus <u>Bodo</u> <u>Monas</u> Order <i>Polymastigina</i> Genus <i>Trepomonas</i> Hexamitus Class RHIZOPODA Order <i>Amoebina</i> Genus <u>Amoeba</u>	3 samples tested Class MASTIGOPHORA Order <i>Protopomonadina</i> Genus <u>Bodo</u> <u>Monas</u> Order <i>Polymastigina</i> Genus <i>Trepomonas</i> Hexamitus Class RHIZOPODA Order <i>Amoebina</i> Genus <u>Amoeba</u> Class CILIATA Order <i>Holotricha</i> Genus <i>Paramaecium</i> Balantidium Glaucoma Cyclidium Order <i>Oligotricha</i> Genus <i>Pleurotricha</i> Order <i>Peritricha</i> Genus <i>Vorticella</i>
Class Schizomycetes			Bacteriaceae, Spirillaceae

as specimens from 10 healthy persons. The observations made up to date have been summarised in the annexed table (Table 1). Several details of interest can be gathered from this survey.

If we tarry first at the findings of *Schizomycetes* noted in the bottom part of the table, we see that the five columns show quite a uniform appearance. In all these kinds of cultures one has been able to note bacteria of all sorts of types, together with spirillaceae and spirochaetes. We have not considered ourselves — at least not until all other possibilities have been exhausted — to have any reason to determine these micro-organisms, for suspicions are in the first instance not directed to one of these elements as acceptable vector for poliomyelitis virus. The various bacteriophages, by many regarded as ultravirus, are, it is true, parasitising on representatives within this class of living beings, but otherwise we do not know any examples of *Schizomycetes* as host organisms for infectious agents. In order to find beings that play such a part one must go to the animal world, and amongst the arthropodes one encounters in fact vectors for several ultravirus diseases (yellow fever, dengue fever, virus infections in certain vegetables, to mention only a few examples now). We can thus for the time being leave the *Schizomycetes* aside.

If we now go farther and turn to the protozoa observed in the different kinds of cultures, — in the table placed after Doflein's system¹ — we find at once a striking difference between the five columns: on the one hand, a great plenitude of species in regard to the water- and sewage-protozoa, a pronounced poverty of species, on the other hand, regarding the stool-protozoa. It is just what we had *a priori* expected as a first result of the investigations.

The cultures from the water-supplies and the sewage display mutually no closer deviations from one another in a qualitative respect. In the former, no fewer than 12 species of protozoa have been identified, 11 of them are also to be found in the latter. The species identified belong to the classes *Mastigophora* (orders Protomonadina and Polymastigina), *Rhizopoda* (order Amoebina) *Ciliata* (orders Holotricha, Oligotricha and Peritricha). In the cultures from water-supplies one finds furthermore no more closely differentiated genera belonging to the order Heliozoa. Since the specimens from water so far investigated are as many as 33, one can get a certain idea of the relative frequency of the species of protozoa most commonly observed in them. In the majority of these specimens we have found species of *Bodo* and *Monas* (in over 80 % of the cases). These organisms have also been existing in the three sewage tests.

What, finally, does the protozoological examination of the different stool specimens tell us, amongst which those derived from poliomyelitis cases in the first instance is of interest? As the table indicates, only two, respectively three, genera of protozoa could be identified in them. In *poliomyelitic stools*

¹ Doflein und Reichenow: »Lehrbuch der Protozoenkunde«, Gustav Fischer, Jena 1928, p. 443.

have been encountered genera of Bodo, Monas and Amoeba, in the *control stools* (from other diseases and from healthy individuals) only the two first-mentioned. To the absence of amoeba in these two last-mentioned categories of stools can hardly be attributed any importance. That we have so far been unable to observe them here is very likely mainly to be considered as temporary, probably due to the comparatively small extent of this test material. The cause may be one or the other, the fact is that *Amoeba coli*, e. g. not rarely has been diagnosed in human stools. A future extension of the control material will surely lead to an elimination of the aforesaid deviation.

Already now we have got so far in the analysis of our protozoa findings, that we are able to discern the common feature of the three different kinds of cultures. For facilitating and prosecuting this comparative examination such forms of protozoa as are throughout found in the cultures in question, have been brought together within a *rectangular* figure. These figures are met with — as we are at once able to establish — around the genera Bodo, Monas and Amoeba. On the conjectured condition that poliomyelitis virus lives and multiplies within either one of these protozoa, it is a matter of making a selection between them. Which is the guilty one, or cautiously expressed, the most suspect? Is it the genus Bodo, Monas or Amoeba? A determination of their mutual frequency should, it seems to us, in this be able to act as a guide. As we have at disposal quite a large number of examined specimens of stools from cases of poliomyelitis, we consider ourselves entitled to make such a frequency calculation. It is the genus Bodo which in incomparably the most common. If one reckons with the total material (specimens of stools collected in both early and late stages of the disease) it is found that it occurred in 51 % of the cases examined, Monas and Amoeba, on the other hand, more seldom (in 14 respectively 15 %). To judge from our latest experience, the genus Bodo is a still more common intestinal parasit during the earliest stages of poliomyelitis, (as also under certain circumstances in other diseases). In 30 specimens of stools from cases of poliomyelitis examined during the period July to September, 1941, and collected, the vast majority, during the first days of the disease (from patients treated at the Isolation Hospital at Stockholm respectively Uppsala) Bodo was diagnosed in no fewer than 73 %, Monas and Amoeba only in 3.3 % of the cases examined.

If Bodo occurs during the early stage of poliomyelitis in high frequency, it seems, on the other hand, to disappear more or less rapidly from the stool. We have not as yet had an opportunity in this respect to make any more thorough investigations, but are already now able to state some interesting figures. 13 specimens of stools containing Bodo were examined afresh after a shorter or longer period. 10 of these specimens were clearly »negative» after 27—29 days; only in three specimens it still existed (after respectively 37, 54 and 55 days). We wish in this connexion to recall that we have been able to demonstrate the presence of poliomyelitis virus in the stools of human beings much more frequently during the first week of the disease than during the later stages of the same (see above). Is the parallel drawn up here merely an expression of an accident or does there perhaps exist a causal connexion? With this we have entered upon the question of the part played by Bodo as a possible intermediary host for the poliomyelitic infection.

It may be opportune to begin with the objections that may be raised to this idea. If these were to prove to be far too onerous, it would, of course, be meaningless to deal further with the same. The protozoon here in question is present, as we have seen, not only in poliomyelitis, but also in other diseases, aye, even in healthy individuals. This fact seems also — with superficial observance — to be of a nature to cause hesitation. But let us ponder a little more closely the assumption.

Everything indicates — both epidemiologically and experimentally — that water-supplies of various kinds constitute important sources for the poliomyelitic infection. It is nevertheless generally only exceptional that these vehicles are contaminated with poliomyelitis virus. During the extensive spread of the disease, in which the infected sewer plays a great part, the condition becomes, on the other hand, a different one; more and more effluences may in this case become contaminated. Even under the said conditions there are, however, major or minor parts of the country where the water, on account of special hydrographic circumstances, remains free from the causative factor. But in spite of this it is not difficult to encounter Bodo flagellates in such areas. These organisms are, of course, as protozoologists tell us, generally occurring in polluted water, whence they easily enter the alimentary canal. Is it, therefore, inconceivable that there exist species of Bodo that

are infected with poliomyelitis virus, and also that there are such — and this in such events the most common ones — that are free from this infection? In our opinion there is nothing unreasonable in such a hypothesis. On the contrary, animal pathology presents sundry examples of such an uneven distribution of infected vectors. We need only remember some diseases in human beings, whose transmission takes place through the intermediary of blood-sucking insects, such as *malaria*, plague and yellow fever. The vectors of these diseases are widely disseminated, but it is mostly only a small percentage of them that are infected. In our country there is at present prevailing *Anophelism without malaria*.

Protozoologists tell us that the genus *Bodo* embraces a large number of species, which only with difficulty can be distinguished from one another. From 44 specimens of poliomyelitic stools there has in cultivation grown a species of *Bodo*, which in size, internal structure, arrangement of flagella and type of movement best coincides with *Bodo caudatus* Dujaric. In only one stool culture has been observed *Bodo saltans*, Ehrbg, and in two cultures of this kind both species were found in combination (see fig. 1). Out of the 33 specimens of water, *Bodo caudatus* has developed seven and *Bodo saltans* 5 times; both species have been seen to occur side by side in 15 cultures. The Stockholm sewers seem to harbour both species. Should the investigations planned (see below) fully verify our assumption, that the protozoon in question plays the rôle of poliomyelitis vector, it would naturally become necessary to make a more thorough study of its position within the genus *Bodo*, as also of its biological conditions — which up to the present are known only incompletely.

This is consequently a first stage of the investigations which we have begun of late for the purpose of finding the supposed vector of poliomyelitis. We have, both in the source of infection (drinking-water of different kinds) and in the stools from individuals suffering from poliomyelitis as also in the recipient for the intestinal excretions (sewage), met with a protozoon, which might possibly play a part as such an intermediary host. It is now a matter of deciding whether this assumption can have a satisfactory foundation or not. What possibilities are available for us to solve this question? The animal experimental path seems open and clear. Here are some hints of our prospective plan of work.

The *Bodo*-organisms observed can easily be cultivated in the medium employed by us and grow also in subcultures, at least up to a certain limit. But this cultivation has so far only been

successful in the presence of Schizomycetes. It is, therefore, protozoologically looked at, so-called mixed cultures that we have had in our hands. These cultures present certain analogies with sewage, in which occur zoo- and phytoplankton of various kinds, and during periods when poliomyelitis epidemics are prevailing, even the agent of this disease. The cultures here referred to can, therefore, be tested for their specific virulence in the same manner as when it is a matter of sewage. One might then, if a positive inoculation result

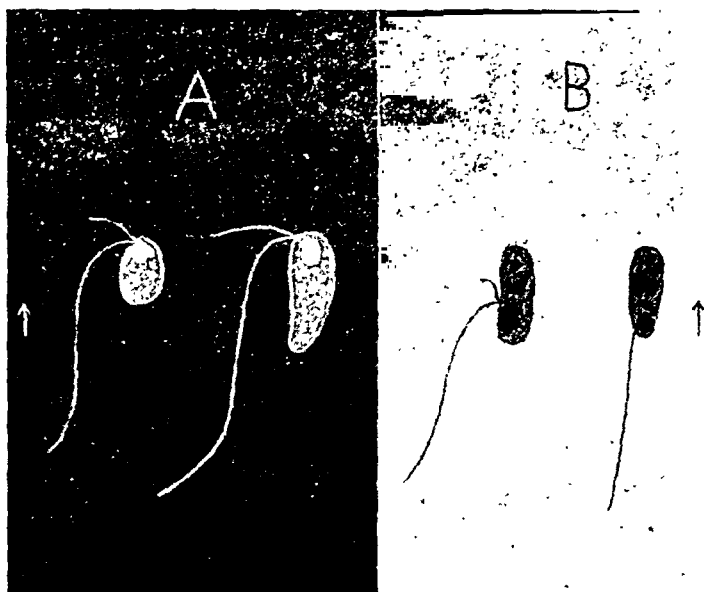


Fig. 1.

Bodo-organisms, observed in cultures obtained from poliomyelitic stools.

A. *Bodo caudatus* Dujaric.

B. *Bodo saltans* Erbg.

were achieved, proceed farther and, after isolating the various elements developed in the culture, try to ascertain their poliomyelitogenic power. It is natural that for our own part in the first instance we devote our attention to the species of Bodo as being the most suspected in the collection. But it may also become necessary to make a general muster of all the elements in the cultures, before full clarity is obtained. In such case there is ahead a vast amount of arduous work, which one should, however, not shrink from, if one has in fact a safe starting point, i. e. a mixed culture that has proved to possess specific virulence. In these tests it should not be

forgotten that experimental poliomyelitis, as we know now, can pass off under *abortive* or, to use another term, «non-paralytic» forms. Other possibilities to illuminate the problem by experiments on animals are also feasible. We refrain at present from dealing further with this matter but wish only to add that for testing our working hypothesis we have for some time been experimenting in the one direction and the other.

Summary.

I. In conjunction with an epidemic of infantile paralysis prevailing in Stockholm in the summer and autumn of 1939 the agent of the disease was searched for in the sewage of the city on three different occasions.

In the first test was isolated from a specimen collected at the height of the epidemic a strain of poliomyelitis virus, which was able to produce in the monkey the paralytic poliomyelitis with typical and intense lesions present in different levels of the central nervous system, and which could be transferred in serial passages.

Three months after the epidemic's total cessation the poliomyelitis virus was detected in the same sewage, but this time with *attenuated* virulence.

In a third test, carried out 9 months after the end of the epidemic — no case of the disease had in the interval been observed in the capital — the virus seems to have disappeared from the sewage, at least in a stage revealable by the ordinary tests.

II. In studying the strains of poliomyelitis virus (VT 51 and VT 57 B) isolated from the Stockholm sewage we have obtained fresh proofs of the fact that experimental poliomyelitis in the monkey can pass under *abortive* («non-paralytic») forms disclosable first in the histological examination of the neuraxis. In accounting for these observations we have communicated some previous ones made. In spite of the absence of apparent symptoms of paralysis, one is able in such animals to reveal the presence of more or less propagated poliomyelitic changes (cerebro-spinal or cerebro-medullary types — *with* respectively *without* the characteristic neuronophagia in the grey matter of the spinal cord).

III. The observations made have shown that poliomyelitis virus can retain its virulence in sewage sediment, which has been stored at a temperature of $+4^{\circ}\text{C}$, for a term of at least 2 to 3 months.

It might, therefore, if regard is furthermore taken to other known facts, be permitted to conjecture that the infectious agent possesses considerable resistance even under *natural* conditions, both in the sewage itself and when issued into the recipient and its different outlets. The sewer itself must clearly be looked upon as an important source of infection, from which virus with retained pathogenicity can be moved for long distances. An important support for the conception of poliomyelitis as a »water-borne disease» has by this discovery been gained.

IV. The knowledge of the presence of the etiologic factor in sewage is, of course, calculated to lead the prophylaxis against poliomyelitis into more rational paths. The champions of hygiene should with this have obtained better possibilities to be able to combat the disease more successfully.

V. The experimental observations made in establishing the presence of poliomyelitis virus in the Stockholm sewage hint at a *massive* infection of the same having existed. The epidemiological inquiry instituted in conjunction with them has been taken as the starting point for a discussion of the question relating to the origin of the specific agent revealed. Two alternative possibilities are being ventilated. One possibility presupposes the presence of a considerable number of *healthy virus carriers* living within the drainage area whence the infected sewage came. The other possibility reckons with a multiplication of the virus after it has been discharged into the sewer by individuals attacked by poliomyelitis. Epidemiological reasons seem to speak in favour of the latter possibility being much more probable. This conclusion issues from the indispensable assumption that there exists a living being, which functions as a vector for the etiologic agent. The supposition has given rise to the inauguration of studies concerning the conditions of life of poliomyelitis virus *outside* the human organism. A first result of the investigation is given. By way of elimination these studies have been directed to the *sewage itself* as a vehicle for the hypothe-

tical organism. The *source of infection* (specimens of different kinds of water), *stools* from cases of poliomyelitis as well as the *recipient* for these human excretions (sewage) have been made the subject for comparative bio-morphological studies. Attention has in the course of these researches been directed to a protozoon (belonging to the genus *Bodo*), towards which there had been cause to direct the suspicions as a possible vector. A programme for examining this working hypothesis has been drawn up.

(From the Lung Clinic at Lund (Sweden) (temporary Physician-in-charge:
Dr Erik von Rosen).

Intrathoracic hypernephroma metastases simulating primary pulmonary disease.

Contribution to the differential diagnosis in cases of hilus
lymphomas. Transpleural gland biopsy.

By

STIG RADNER.

(Submitted for publication June 3, 1942).

A malignant renal tumour usually announces itself by one or more of the symptoms which constitute the classic triad: hematuria, pain and palpable tumour. It appears from several considerable collocations that hematuria, either by itself or associated with pain, is the initial symptom in more than half the cases. Pain conditioned renally is stated to be the first symptom in about one-third of all cases. Not infrequently the disease manifests itself for the first time as a palpable abdominal tumour; this occurs on an average in somewhat more than 10 % of the cases published.

There is also, however, a smaller group where the initial symptomatology of the renal tumour may present considerable diagnostic difficulties for the clinician. This group comprises principally such cases as those in which the latent primary tumours make their first appearance with localised secondary symptoms from other organ systems. The pathological-anatomical basis for these atypical manifestations is represented partly by a local propagation from the primary tumour, encroaching on the surrounding organs, partly by metastases. The majority of casuistics published contain observations of this kind. There are very different statements in

the literature as regards the frequency of malignant renal tumours with foreign organ disease as the first symptom. In general it is a matter of a small number per cent, but considerably higher figures have also been given.

It is an extremely varied clinical symptom picture that may arise on the basis of such secondary organ changes with an otherwise not manifest malignant renal tumour.

By means of direct propagation of the primary tumour to the organs which have a topographical relation to the kidneys, manifestations are evoked from the colon, ventricle, jejuno-ileum, gall ducts and vena cava inferior system.

In this connection the metastases and the apparently primary morbid pictures provoked by them are of greater interest. When going through the relevant literature one finds that metastases may be deposited in practically all the organs of the body. The place of predilection is the skeleton system — a fact which, according to Ask-Upmark (1938), is possibly due to the property of the bone marrow as the largest parenchymatous organ of the body with the relatively most powerful reception surface for a hematogenous metastatic dissemination. It is just the skeleton metastases that form the chief part of the group with secondary manifestations in the case of latent primary tumours. Thus, in that group a malignant renal tumour may make its first appearance under the picture of a bone swelling, giving the impression of being primary, a spontaneous fracture or a compression myelitis.

The next most usual localisation of daughter tumours from malignant renal tumours is the lungs and their adnex organs. Within these organs metastases make their appearance in the lung parenchyma, pleurae and the regionary lymphatic glands. The secondary tumours situated in the lung parenchyma not infrequently remain clinically latent for long periods, and not until they begin to attack the pleural sac or the bronchi by means of further propagation do clinical manifestations of the changes appear. With a metastatic involvement of the regionary lymphatic gland groups adjacent to the bronchial tube, the conditions for their compression are present with signs of bronchial stenosis as a result. There is no clinical symptomatology from the respiratory organs which is specially characteristic of renal tumour metastases. Persistent desire to cough, blood-tinged sputa, pains and »stitch» in the

chest are the troubles in these cases. Neither do the changes present any characteristic picture from the roentgenological point of view: well-delimited, discrete at first, but later confluent, ball-shaped infiltrations in the pulmonary areas, at times together with moderately enlarged hilus glands. This picture is also met in the case of intrathoracic metastases from a number of different forms of tumour.

Thus, although a relatively large number of the daughter tumours disseminated from the renal tumour are deposited in the lungs, it is very unusual for symptoms arising from these tumours to constitute the first sign of the primary tumour. This was the case, however, in the observation which forms the starting-point for the present paper. In the available literature on the subject only six similar observations are met with, of which 1 was published by Gottesman, Perla and Elson (1932), 1 by G. P. Muller (1934), 3 by Creevy (1935), and 1 by Pendergrass and Hodes (1936). Creevy states, however, that he has observed a further 8 cases of this type, but gives no description of them.

In comparison with the frequency of metastases to the skeleton system and lungs, this frequency is considerably less for the other organs. This applies also to the symptoms simulating primary organ diseases evoked by the metastases, which are of particular interest from the present point of view. There are casuistic reports of such symptoms from different organs, but — with the exception of the central nervous system — these are pure curiosities.

In the group of cases with atypical manifestations with for the rest latent renal neoplasm sketched above is included finally a smaller series of observations where fever, emaciation, fatigue and other non-localised secondary symptoms are the only clinical sign of the presence of the tumour.

In association with the preceding description of the atypical symptomatology in cases of malignant renal tumours, an account will first be given of a case of intrathoracic hypernephroma metastases simulating primary pulmonary disease. This case gave us great diagnostic difficulties, and the patient died without the nature of the changes being identified. The connection with the clinically latent primary tumour was not discovered until the autopsy.

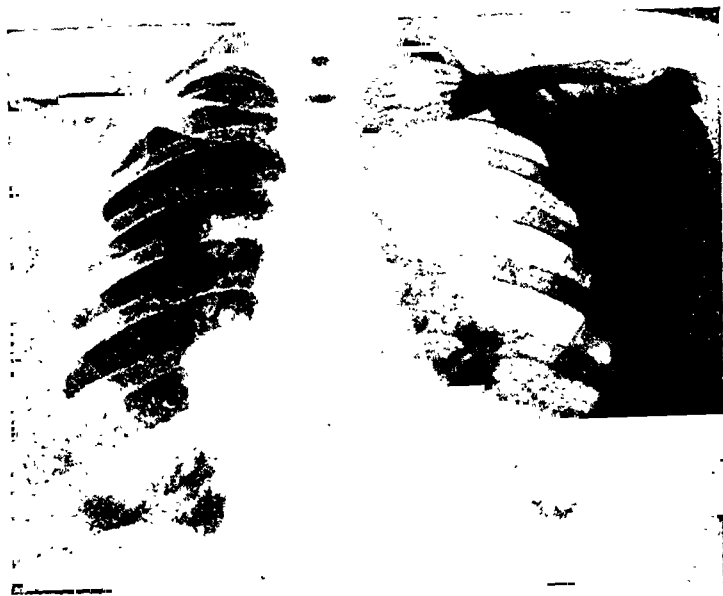


Fig. 1. 39-year-old woman. Cough for 3 months owing to intrathoracic hypernephroma metastases from an otherwise latent primary tumour.

The case-record at the Lung Clinic 55/1942. Mrs J. J. aged 39.

Anamnesis. Nothing of interest hereditarily. No known exposure to tbc. Has always been healthy for the most part. The patient was the mother of 4 children, of whom the youngest was 2 ½ months old when the patient was admitted. During the last pregnancy, at the fifth month, symptoms of catarrh of the bladder made their appearance, which receded after treatment. In association with the catarrh of the bladder there was albumen in the urine. Some days after her delivery, a brief rise in temperature was observed, which persisted for about 24 hours.

In September 1941, during the last month of pregnancy, the patient began to be troubled by an irritable cough with slight expectoration. For the rest felt well and was able to look after her home. No trouble from the abdomen or urogenital organs. Occasionally had night sweats but did not take her temperature. The desire to cough increased, and the patient began to lose weight. She therefore consulted a doctor, who established morbid changes in the lungs and on 16th December 1941 sent the patient to the Central Dispensary in Lund. Roentgen screening here (author) revealed pronounced bilateral enlargement of the hilus glands with polycyclic lateral limits. Above the right hilus a rounded induration the size of a walnut, and basally on the right side a smaller, well-defined spot, which, however, proved to correspond to the mamilla, were observed. In the left Ics II and III a couple of parenchymal changes the size of a couple of finger-tops were seen. The appearance is shown by the attached roentgen picture (see fig. 1) taken at the Roentgen Diagnostic Department at Lund (Physician-in-charge: Dr H. Hellmer).

In view of the result of the examination, the patient was admitted to the Lung Clinic on 16th January 1942.

Status on admission. Good general condition. No cyanosis or dyspnoea during rest. Normal heart findings. The physical lung examination revealed no pathological conditions within the thorax, apart from occasional ronchi on both sides. No foreign resistance could be established on abdominal palpation. Farthest up in the left axillary fossa a firm, non-tender, movable gland the size of a bean was felt, and in the right groin a similar gland, but for the rest the superficial lymphatic glands were without remark.

At first the temperature was subfebrile but later rose with indicated periodicity on a couple of occasions. When the patient was admitted, the sedimentation rate was 48 mm/1 hr. and fell after 3 weeks to 36 mm. Blood pressure: 140/95 mm Hg. The number of white blood corpuscles increased during the course of the illness from 10,700 to 19,200. The differential count showed an increase of the eosinophil elements, and their highest value was 12 %. There was further a relative lymphopenia with 9 % lymphocytes as the lowest value.

In the sediment of urine there were no pathological constituents apart from occasional white blood corpuscles. No albumen in the urine.

A tuberculin test with Mantoux 0.01 mg gave a negative result, but the reaction was positive with 0.1 mg (15×20 mm).

No tbc. bacilli could be proved either in direct preparations of the sputum or in guinea-pig tests with the gastric lavage fluid.

The pathological-anatomical examination of a test excised inguinal gland gave no indications of a pathological process within the gland.

Sputum tests were examined for tumour cells, but without definite results.

On admission, 1 month after the first examination, a clear progress of the changes both in the hilus glands and in the parenchyma was established on the roentgen picture.

Course. During her stay in hospital the patient's condition underwent a continuous disimprovement. In connection with a couple of periods of high fever, diffused cloudy parenchymal changes were observed roentgenologically within both lung areas, and at the same time physical signs of parenchymal infiltration appeared. The patient exhibited an increasing cyanosis and became dyspneic with sub finem stridulous respiration. The desire to cough increased gradually, and the expectoration became tinged with blood. The course was complicated by a thrombophlebitis in the region of the right knee with oedematous swelling of especially the right, but also of the left lower leg, indicating the engagement of the deep veins. During the last week the patient complained of weakness in the right hand and exhibited objectively a flaccid paresis in it. No other neurological symptoms were present. A further roentgen examination 3 days before mors revealed a further progress of the intrapulmonal changes (see fig. 2). The patient died on 16th February 1942.



Fig. 2. Same case 2 months later.

Pathological-anatomical examination (Dr C. G. Ahlström).

Diagnosis: left-sided hypernephroma; metastases within the retroperitoneal and mediastinal lymphatic glands and within the lymphatic glands at the lung hilus; multiple, more recent metastases within both lungs, especially the right; metastatic dissemination on the pleura visceralis bilaterally; metastases within both suprarenal glands. Multiple bronchopneumonias. Superficial thrombi on the right thigh; hemorrhagic infarct within the right upper lobe of the lung.

When the bronchial tree on the right side was cut open, both the lower and the upper main bronchi proved to be constricted by a white tumour infiltration within the bronchial mucous membrane. The tumour infiltration had its point of departure from rounded massive tumour foci lying outside the bronchus, which were situated close up to the hilus and constricted the bronchi in a one-cm.-long section. The bronchial branches to the central area of the lung exhibited no constriction.

No metastases within the central nervous system.

Microscopic examination. The renal tumour exhibits a typical picture of a hypernephroma built up to considerable polyadral cells with abundant clear cytoplasm, containing somewhat abundant lipoids; within some areas the cell picture is more polymorphous. Fairly pronounced infiltrative growth with ingrowths in the vessels.

The metastases in the lungs show, in principle, the same picture as the primary tumour.

The hilus glands are partly studded with tumours, but their increase in size is partly conditioned by an unspecific inflammatory irritation; probably secondary to the extensive pneumonias.

Summary. A 39-year-old woman, who had previously always been healthy on the whole, consults a doctor for an irritating cough, which she has had for 3 months. A roentgen examination reveals pronounced bilateral hilus gland enlargements and changes in the lung parenchyma of limited extension. Clinically she exhibits fever, moderately increased sedimentation rate and eosinophilia and relative lymphopenia. Other clinical and bacteriological and laboratory examinations give negative results for the most part. On the roentgen picture of the lungs the changes show progress, and finally there is an extensive, bilateral parenchymal affection. The condition undergoes a continuous deterioration with increasing cyanosis, dyspnoea and cough. The patient dies without any clinically established diagnosis having been made.

Autopsy reveals a left-sided hypernephroma with extensive metastases in the lung parenchyma and hilus glands, and complicating bronchopneumonias.

Epicrisis and differential diagnosis.

The case is interesting from several points of view. It provides a further contribution to the diversified symptomatology in cases of latent primary renal tumours with diseases in other organs as the first symptom.

These observation also provide a contribution to the differential diagnosis in cases of hilus lymphomas. In this respect attention should of course be paid to any existing parenchymal changes, the roentgenological structure of which may often facilitate judgment. A number of different etiological possibilities were considered in the present case.

Primary tuberculosis is the most usual cause of bilateral hilus gland enlargements, but makes its first appearance with simultaneous bilateral parenchymal components only in exceptional cases. In our patient the right-sided parenchymal induration was considerably larger than the usual »lobular« order of magnitude in primary tuberculosis. As also the tuberculin reaction was not positive until Mantoux 0.1 mg was employed, and bacilli could not be proved, a tuberculous etiology did not appear very probable.

The picture conformed in casu more to an intrathoracic *lymphogranulomatosis*, and it was under this probable diagnosis that the patient's body was sent for autopsy. From illustrated publications

on the subject it appears that this disease may exhibit a roentgenological picture resembling the one in the present case. The eosinophilia, lymphopenia and fever with its indicated periodicity, might be interpreted in the same sense. The absence of general lymphatic gland swellings does not negative the diagnosis, as lymphogranulomatosis, like other system diseases, may be localised.

The possibility of a *neoplasm* was also considered. Starting from the assumption of a common etiology for the changes in the lung parenchyma and hilus glands, the picture might have been apprehended as a bilateral primary bronchial cancer, with lymphogenous metastasization to the regionary glands in the lung hilus. A bronchoscopic examination would possibly have thrown light on this point, but the patient's fever and increasingly affected condition formed a relative contra-indication for the measure. While the type of bilateral lung cancer mentioned is comparatively unusual, the bilateral metastatic lung tumours constitute an everyday phenomena in clinical practice. It is also known that these tumours in their turn give rise at times, by way of a lymphangitis carcinomatosa, to metastatic involvement of the regionary hilus glands, and in the present case such a possibility could not be excluded. On the first roentgen picture (see fig. 1), however, the hilus lymphomas predominated, so that it appeared improbable that they would be secondary to the relatively limited parenchymal processes.

The apprehension of the metastases in the parenchyma and glands as phenomena independent of each other is confirmed by the following two cases, in which intrathoracic hypernephroma metastases were first deposited in the hilus glands. In both cases nephrectomy had been performed earlier, and both were post mortemed, the character of the gland changes proved roentgenologically also being identified. As similar roentgen pictures do not appear to have been reproduced in earlier literature, the pictures referring to the cases are given.

Case 1. Surg. clin. case record 667/1931. Mr N. L. aged 53 years.

In March 1931 right-sided nephrectomy was performed, and the pathological-anatomical examination showed a hypernephroma. Already 4 months before the op. right-sided hilus gland enlargements had been observed, which gradually increased in extension, and 13 months after the op. exhibited a picture as shown by fig. 3. In the after-course metastases also appeared in the skeleton system. Death in June 1932. At autopsy the hilus glands proved to be studded with hypernephroma metastases.



Fig. 3. 53-year-old man. Previous nephrectomy owing to hypernephroma. Metastases in the hilus glands on the right side.

The roentgen picture was taken at the Roentgen Department at Lund (late Physician-in-charge: Dr L. Edling).

This case appears as no. 67 in S. Bergendal's (1935) casuistics of renal tumours collocated from a different point of view from the present one, and without the reproduction of roentgen pictures.

Case 2. Med. clin. case record 1283/1938. Mr V. B. aged 58 years. In December 1937 right-sided nephrectomy was performed on account of hypernephroma. After the op. well until March 1938, when he fell ill with fever of a periodic type. Roentgen examination of the lungs in April the same year showed metastases in the hilus glands on the right side (see fig. 4). Later slight parenchymal changes appeared and also a right-sided hemorrhagic pleuritis. Death in February 1939 at another hospital. Autopsy confirmed the metastatic nature of the hilus changes observed roentgenologically.

The roentgen picture was taken at the Roentgen Department at Malmö. (Physician-in-charge: Dr D. B. Carlsten).

This case has been published earlier in another connection and without roentgen pictures by Ask-Upmark (1938).

At the ordinary clinical examination of the present case the primary tumour could not be proved. Thus, no pathological resistances could be felt in the abdomen. This is not infrequently the case with renal tumours, especially if they are localised in the upper pole. In Bergendal's (1935) material there were negative pal-



Fig. 4. 58-year-old man. Previous nephrectomy owing to hypernephroma. Metastases in the hilus glands on the right side.

pation findings in 14 of the 76 cases with such tumours. The urine finding was also negative, and from the relevant literature it appears that the urine may be free from abnormal constituents in, e. g., 5 cases out of 18 (Albrecht, 1905). The absence of clinical manifestations on the part of the primary tumour had the result that the idea of intrathoracic metastases did not suggest itself, even though the picture could have been interpreted as an atypical form of metastasization.

The course of the disease in the present case assumed a rapidly progressing character. Certain benignant hilus gland affections were therefore soon excluded as pathogenetic possibilities. Otherwise bilateral unspecific *bronchopneumonias* with regionary hilus gland reactions might have been one such possibility. Apart from the course of the disease, our case differed from *lymphogranulomatosis benigna* also in respect of the simultaneous parenchymal changes, which were not of the punctate type which characterizes that form of disease.

Finally, an intrathoracic *leukaemic lymphadenosis* may give rise to roentgenologically provable hilus enlargements. Differential counts of white blood corpuscles, or bone-marrow punctures decide the matter in this respect.

The differential diagnostics in the case of hilus lymphomas thus comprise a series of diseases of a varied nature. Our methods of examination are restricted here, and at times the clinical diagnosis is uncertain. When it is a matter of superficial groups of lymphatic glands, enlightenment may be obtained in many cases by means of tissue biopsy and pathological-anatomical examinations. The hilus lymphomas visible on the dorsoventral roentgen picture correspond mainly to the bronchopulmonary gland groups and are situated intrapulmonarily. They are therefore inaccessible for biopsy.

Adjacent to the main bronchi on the area between the anatomical hilus and the trachea are, however, the tracheo-bronchial lymphatic glands, whose localisation against the pleural cavity makes them accessible for transpleural surgical measures. These glands emerge on the dorsoventral picture only if they are considerably enlarged (Westermarck, 1940), and therefore correspond to only a lesser part of the hilus lymphomas proved roentgenologically. As in the case of other groups with the same inter-relationship, a simultaneous affection of the bronchopulmonary and tracheo-bronchial gland groups is probably very usual. Thus, at autopsy, in the case under discussion the glands last-mentioned were observed as packets of the size of walnuts immediately mediastinally of the anatomical hilus. In the case of hilus lymphomas of uncertain etiology determined roentgenologically, it should therefore be possible in many cases to perform a *transpleural gland biopsy* of the tracheo-bronchial groups. This operation presupposes a collapse of the lung by means of diagnostic pneumothorax. A test excision is then made in association with thoracoscopy in a manner which has earlier been described by various authors dealing with subpleural lung tumours.

In the case before us a transpleural gland biopsy was performed (the present author) post mortem, a simplified set of instruments being used. A cannula was inserted on the dorsal side on a level with the lung hilus 8 cm to the left of the spinal process. Through this cannula were then inserted a light mounted in the point of a metal rod and a test incision forceps of the ordinary »alligator» type used in bronchoscopic practice. The pieces of tissue obtained in this way were sent for pathological-anatomical examination, and the following expression of opinion was given (Dr C. G. Ahlström):

Within both test excisions from the hilus glands taken at the post-mortal thoracoscopy the picture of a hypernephroma tissue is seen; without any knowledge of the primary tumour it would, however, be hardly possible to venture anything more definite than the diagnosis »malignant tumour», as the arrangement of the tumour cells within the hilus metastases is not characteristic, and there are no streaks of fat in the cytoplasm.

Since this case, and in view of the discussion provoked in connection with it, we have considered the possibility of also obtaining the diagnosis in vivo, according to the method described.

Transpleural gland biopsy is naturally not suitable for routine examinations in the case of enlarged hilus glands. Its use is limited to the cases in which it is urgent from the therapeutic and prognostic points of view to obtain the most definite diagnosis possible.

Summary.

1. After a survey of the symptomatology in cases of malignant renal tumours, the author describes a case of hypernephroma, in which the pulmonary symptoms arising from metastases represented the only clinical manifestation from the primary tumour, which was otherwise latent. Roentgen examination revealed pronounced bilateral hilus gland enlargements and parenchymal changes of, at first limited, but gradually increased diffusion. The patient succumbed without a certain clinical diagnosis having been reached. The metastatic nature of the intrathoracic changes was not proved until the autopsy.

2. With this observation as a starting-point, the differential diagnosis in the case of hilus lymphomas observable roentgenologically is discussed. In connection with this two cases are described in which intrathoracic hypernephroma metastases on the roentgen picture made their first appearance in the hilus glands, without simultaneous parenchymal changes.

3. Finally, a method is indicated for examining etiologically unelucidated hilus lymphomas: transpleural gland biopsy.

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Iron Content of the Serum in Lesions of the Liver and Bile Passages.¹

By

KNUD BRØCHNER-MORTENSEN.

(Submitted for publication June 15, 1942).

In recent years a number of investigators have shown that the iron content of the serum is often increased in patients with acute hepatitis, whereas this is a rare finding in patients with obstructive jaundice.

Among the earliest investigators of the iron content of serum, Warburg & Krebs (13), working with Warburg's cystein method, found already in 1927 that the serum iron was increased quite considerably in a patient with jaundice.

The subsequent investigations have been carried out mostly after Heilmeyer & Pløtner's (4) phenantrolin method. The estimation of the analytical results by the various authors has varied somewhat with their view concerning the limits for the normal range of variations for the iron content of serum. Gradually, however, it has become the prevailing view that values over 200 γ % are found but seldom on examination of normal subjects. The lower limit is not so definitely established, some authors setting it at 80 γ %, others at 50 γ %.

¹ The studies here reported were carried out with the aid of a grant from the Christian X's Fond.

Table 1.

Previous Studies on the Iron Content of the Serum in Patients with Lesions of the Liver and Bile Passages.

Author	Year	Acute hepatitis				Obstructive jaundice			
		No. of patients examined	Serum iron γ %			No. of patients examined	Serum iron γ %		
			<80	80—200	>200		<80	80—200	>200
			No. of patients in each group				No. of patients in each group		
Hemmeler (5) ..	1939	10	0	5	5	11	4	6	1
Skouge (10)	1939	5	0	3	2	4	2	2	0
Waldenstrom (12)	1940	9	0	5	4	—	—	—	—
Vahlquist (11) ..	1941	25	?	?	10	—	—	—	—
		49			21	15			1

The outcome of the previous series of examinations is recorded in Table 1.

In repeated examinations of patients with acute hepatitis, Hemmeler (5) sometimes found a late increase in serum iron. In children, Vahlquist (11) found the serum iron values on an average to be highest in the first week of illness, though subject to great individual variation, in a few cases the maximum was not reached till the 20'—29' days of illness. In some cases the increase in serum iron persisted after the bilirubinemia had subsided.

Writer's investigations.

Material.

The material comprises 50 patients suffering from lesions of the liver and bile passages: 26 with acute hepatitis, 5 with cirrhosis of the liver, 12 with obstructive jaundice from cancer, and 7 with cholelithiasis. Of these patients, 33 were admitted to Dep. II of the Kommune Hospital, and represented all the patients of these groups admitted to the department in two limited periods. Of the remaining patients, 7 were admitted to Dep. III of the same hospital, 5 to Dep. V and 5 to Dep. VII¹, and were picked out at random from the materials of these departments.

¹ The writer is obliged to the chief physicians of these departments — Dr. Poul Iversen, Dr. T. Knudtzon and Dr Hans Heckscher — for permission to examine the patients.

Technique.

Serum iron: Brøchner-Mortensen & Olsen's (2) method.

Icterus index: Meulengracht's (7) method.

Quinine-resistant lipases in serum: Rona's method as elaborated by Polack (8) and Genner (3).

Galactose tolerance test; Bauer's method. Analysis after Schugt (9).

Hemoglobin determination: In hydrochloric acid hematin in Autenrieth-Königsberg's colorimeter corrected after Haldane (100 % = 18.5 vol. % oxygen-combining capacity).

Results of examinations.

The total results of these examinations are given in Table 2. The values obtained for serum iron and icterus index on the first examination are presented graphically in Fig. 1, which also shows the distribution of the values for serum iron observed at a previous examination (2) of 40 normal persons.

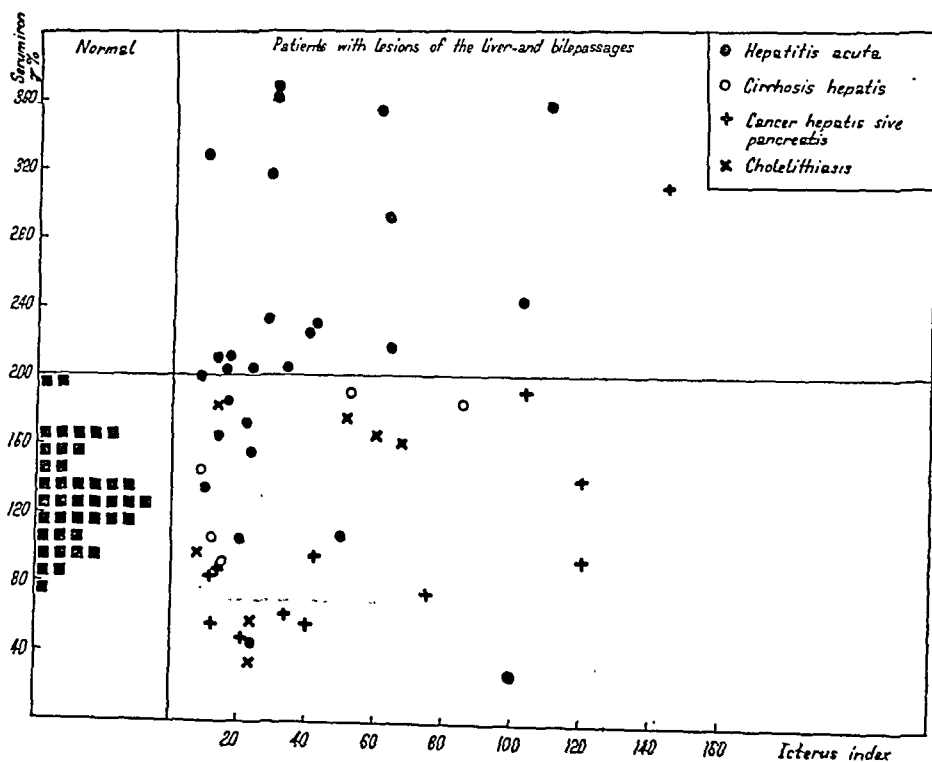


Fig. 1. Iron content of serum in normal persons and in patients with lesions of the liver and bile passages (first Examination).

(Table 2. cont. 1).

Pt. No.	Department and Case Record No.	Sex	Age (Years)	No. of days after appearance of jaundice	Serum iron %	Hemoglobin %	Icterus index	Lipase value	Galactose test— g. of galactose excreted	Temperature level *)
12	II 55—2/41	M.	19	6	215	112	64	12	0.3	0
				13	240	104	30			0
13	II 26—5/41	M.	35	3	210	96	17			0
14	II 48A—8/41	F.	29	14	207	88	14	10	2.1	0
				24	123		6	8		0
				30	94	83	8			0
15	II 453/42	M.	38	13	205	101	16	7	2.8	0
				17	253		14			0
				23	200		6			0
					456 **)					
					400 ***)					
16	II 100—4/41	F.	13	8	204	97	34			0
				15	277	97	11			0
				21	270	97	8			0
17	II 30—11/41	F.	56	15	202	86	23	16		0
18	II 555/42	F.	44	6	199	97	9	6	0.3	0
19	VII 236/41	M.	27	15	183	99	17		2.3	0
20	II 84—10/41	M.	16	18	172	95	22	9		0
				23	156	90	12	14	2.2	0
				29	158	97	9	2	3.7	0
				35	74	96	9	6		0
21	II 105—10/41	M.	11	5	163	90				0
				13	161	87	14	15		0
				18	178	88	9	2	2.4	0
				24	105	90	7			0
22	II 1A—9/41	M.	32	8	155	105	24	10	2.6	I
				18	201	97	70	13		0
				21	169	100	100	1		0
				31	186	92	96	8	3.2	0
				36	185	88	52	5		0
				44	200	88	28	6		0
				50	281	88	22	2		0
				60	102	90	18	7		0
				65	150	92	11	3		0
				70	83	94	11	3		0
23	VII 151/41	F.	41	6	132	80	10		3.3	5
24	II 7—1/41	F.	19	2			60			0
				7	107	100				0
				12	118	93	45			0
				19	160	86				0
				26	153	95	20			0
				33	118	93	14			0
25	II 31—10/41	F.	26	4	103	85	20	18	4.6	II
				11	125	85	19	2		0
				16	147	84	11	16		0
				25	141	88	7	9	2.8	0
26	III 326/41	M.	33	3	42	91	23			I

(Table 2. cont. 2).

Pl. No.	Department and Case Record No.	Sex	Age (years)	No. of days after appearance of jaundice	Serum iron %	Hemoglobin %	Icterus index	Lipase value	Galactose test— g. of galactose excreted	Temperature level *)
<i>Cirrhosis of the liver.</i>										
27	II 65—1/42	M.	14	ca. 170	190	80	52	9	2.2	0
				175	146	75	30	5		0
				181	207	75	31	6	9.1	0
				188	177	71	27	11		0
				198	206	73	21	8		0
28	II 132—10/42	F.	70	38	182	86	85	7		0
				45	122	83	96	15		0
				56	165	78	44	8		0
29	II 138—7/41	M.	59	7	145	81	9			I
30	III 515/41	M.	47	?	106	88	12			0
31	II 505/42	M.	56	54	92	62	15	3		0
<i>Cancer of the liver or pancreas with stenosis of the common bile duct.</i>										
32	II 44A—10/41	M.	55	20	268	95	144	12	0	I
				26	176	85	152	5	1.7	I
				33	178	78	124	13		I
				39	139	78	224	2	0	I
				49	95	80	224	10		I
				54	94	76	210	3		I
				60	69	75	160	3	1.4	I
				66	82	75	165	8		I
33	II 34—7/41	M.	73	13	190	83	104			I
34	II 131—11/41	M.	46	6	140	69	120		5.8	I
				13	77	58	172	13		I
				18	102	54	184	9	1.2	I
				26	57	57	112	15		I
				32	84	68	120			I
				42	91	70	52	12		
				47	48	74	95	7		
				53	102	75	85	15		
				59	94	75	92	10		
				69	95	78	115	6		
35	V 896/41	M.	55	21	95	98	42		0.2	II
36	II 552/42	M.	60	40	95	93	120	8	9.9	0
37	II 78A—9/41	F.	67	ca. 400	91	74	14	3	0	0
38	II 81/42	M.	67	45	87	75	12			0
39	V 48/41	F.	60	54	75	92	75			II
40	II 139—5/41	M.	72	2	66	87	40			0
41	V 1052/41	F.	67	34	61	73	34		1.8	I
42	III 360/41	M.	63	15	59	88	12		0	0
43	II 133—1/41	M.	58	55	47	82	21			II
<i>Cholelithiasis.</i>										
44	V 635/41	M.	43	6	181	110	15			0
45	VII 231/41	M.	47	20	175	110	52		2.6	I
46	VII 380/41	M.	63	38	165	80	60		6.8	I
47	II 25—7/41	M.	72	38	160	85	68			I
48	II 106—5/41	F.	65	?	99	84	9		0	0
49	II 75A—9/41	F.	55	3	59	81	24	15		III
				10	95	83	9	9	0.4	0
50	III 315/41	M.	35	19	33	91	23		0.7	0

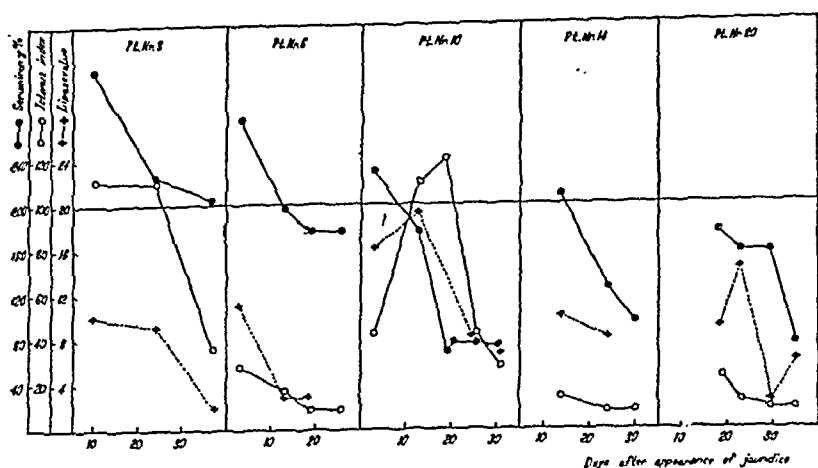


Fig. 2. Variations in serum iron, icterus index and lipase value in patients with hepatitis.

In 26 cases of *acute hepatitis*, determination of the serum iron was performed from 1 to 12 times — altogether 80 determinations.

On the first examination, 17 of these patients (65 %) showed values over 200 γ %, which is taken to be the upper limit for the normal range of variations. At the same time, the icterus index was between 28 and 110 in 12 patients, between 10 and 23 in 5.

In 8 patients the first examination gave values between 103 and 199 γ %, i. e., within the normal limits. Two of these patients were febrile, however, and one of them showed later an unquestionable increase in serum iron (up to 281 γ %). In the remaining 7 patients the degree of the lesion was fairly mild (icterus index between 9 and 22).

Finally, 1 patient showed an unquestionable fall in serum iron, namely: 42 γ %.

Pt. No. 26. Male, aged 33. Diagnosis: *Diabetes mellitus; Incipient coma; Acute hepatitis.*

In 1922, diabetes mellitus, treated with insulin. On admission, incipient coma, jaundice was ascertained (Icterus index 80, subsiding to 10). Temperature subfebrile. Sedimentation rate: 21 mm/1 hr. Urine: + urobilin; + bilirubin; later, no bilirubin.

Biopsy of liver: Typical hepatitis.

In 12 of the patients, 3—12 determinations of serum iron were performed in the course of the illness, most often at intervals of about 1 week. Figs. 2—4 give the variations in serum iron, icterus

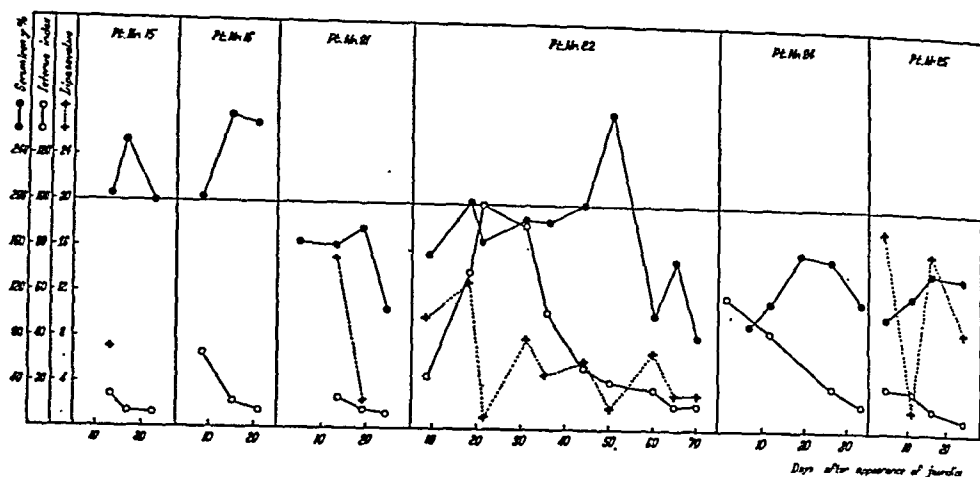


Fig. 3. Variations in serum iron, icterus index and lipase value in patients with hepatitis.

index and lipase values plotted in relation to the duration of illness reckoned from the appearance of jaundice.

From these figures it is seen that the icterus index and, especially, the lipase value as a rule reached their maximum rather rapidly and then subsided at a varying rate, whereas the variations in serum iron content were often somewhat more protracted.

In 5 of these patients (Fig. 2) the maximum value for serum iron was observed already on the first examination (respectively 10, 3, 3, 14 and 18 days after the appearance of jaundice). After this, the values subsided at a variable rate. In one of these patients (No. 10), the fall in serum iron was undoubtedly promoted by a complicating febrile pyelitis.

In 6 of the patients (Fig. 3), who were examined for the first time respectively 13, 8, 5, 8, 7 and 4 days after the appearance of jaundice, the serum iron was seen to increase in spite of the falling values of icterus index. In these cases the highest serum values were observed respectively 17, 15, 18, 50, 19 and 16 days after the appearance of jaundice.

In one patient (Fig. 4), who was not examined till about 1 month after onset of illness, the maximum value for the icterus index was found about 50 days after the appearance of jaundice, while serum iron kept at a fairly constant high level, with maximum on the 38' day. After the icterus index had fallen off considerably, the serum iron concentration kept at a level of the upper normal limit or, most often, a little higher.

On the whole, the greatest values for serum iron were seen in the first weeks of illness — though in several cases not until the icterus index had commenced falling off. As a rule, the fall in serum iron is lagging somewhat after the fall in icterus index and especially in

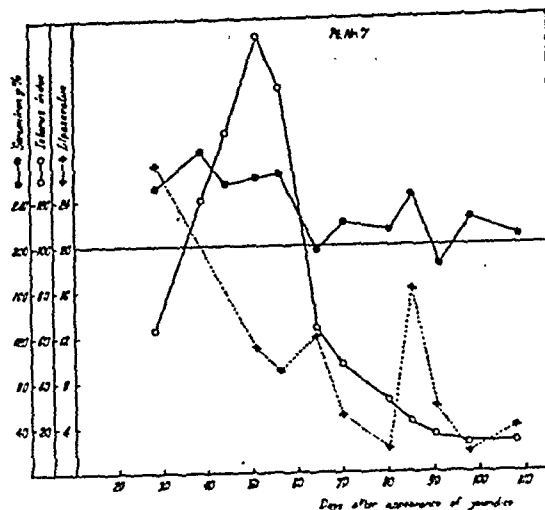


Fig. 4. Variations in serum iron, icterus index and lipase value in a patient with hepatitis.

lipase value. Still, serum iron very often reaches normal values long before the icterus index has become normal.

Of the values here reported, the lipase value as a rule is the first to become normal again — *i. e.*, at a point of time when the icterus index often is increased considerably. Therefore, the examination for quinine-resistant lipases in serum is of particular value in early examination of the patients. Probably this method of examination has been adopted only to a slight extent because its significance early in the disease has not been realized generally.

Determination of the lipase value was performed in 14 cases. Markedly increased values (over 10) were found in 10 patients, slightly increased values (7—10) in 3 patients, and normal value in 1 patient.

Among the 8 patients showing normal values for serum iron, the lipase value was increased in 3, normal in 1.

The galactose tolerance test was performed on 19 patients. In 8 the excretion was found to exceed 3g (but in 2 of these cases the great increase was seen only after repeated examinations, in 6 the excretion amounted to 2—3 g, and in 5 it was less than 2 g.

Among 8 patients with normal values for serum iron, 3 showed a galactose excretion of more than 3 g, while 2 excreted between 2 and 3 g, and 1 only 0.3 g.

All the patients showed urobilinuria.

In 5 patients with *cirrhosis of the liver* (verified on autopsy in 4 cases) 11 determinations of the serum iron were performed. One of these patients, who was examined 5 times at an interval of about 1

week, showed twice a value over 200 γ % (206 and 207 γ %). In the remaining 4 patients the values varied between 92 and 190 γ %, *i. e.*, within normal limits.

In 3 patients the icterus index was between 19 and 15, while in 2 it varied between 21 and 96 (repeated examinations).

The galactose tolerance test was performed only in one patient who showed a great excretion.

The quinine-resistant lipase content of the serum was found to be normal in 1, increased in 2 (on repeated examination, in varying degrees). No definite relation was seen between the variations in lipase value and serum iron. All the patients showed urobilinuria.

In 12 patients with *obstructive jaundice due to cancer* (verified on operation or autopsy in 11) altogether 28 determinations of serum iron were carried out. In 1 patient the first examination showed a serum iron content of 268 γ %, whereafter the values were falling off (see below).

In the remaining 11 patients, the first examination gave values between 47 and 190 γ %; in 5 of these patients the values were under 80 γ %.

On simultaneous determination the icterus index was found to be from 34 to 184 in 8, from 12 to 21 in 4.

The temperature was elevated in 7 of the patients, 2 of whom, together with 2 afebrile, showed a hemoglobin percentage under 80.

In 2 of the patients the serum iron concentration was determined respectively 10 and 8 times, at intervals of about 1 week.

In one of these patients (No. 34), the serum iron varied between 48 and 140 γ %, the icterus index between 52 and 184, the lipase value between 6 and 15, and the hemoglobin percentage between 57 and 78. Apparently there was no relation between the variations in these 4 values.

In the other patient (No. 32) the first determination of serum iron showed 268 γ %; while the following gave normal or subnormal values.

The symptoms commenced 3 weeks before admission, with vague dyspeptic phenomena. One week later there was a slight elevation of the temperature, accompanied by jaundice.

On admission, the patient, whose nutrition was fairly good, showed pronounced jaundice. The liver extended 3 fingers' breadth below the costal margin.

Sedimentation rate: 1 mm/1 hr. Hb.: 95 %. Icterus index: 114. Lipase value: 12. Galactose tolerance test: No excretion. Urine: + urobilin; + bilirubin. Roentgenography showed no concretions in the bile passages.

During the further course of the illness the serum iron concentration fell off to low normal or subnormal values. The hemoglobin percentage fell off, too. The icterus index rose to 224, and then it fell off again. The sedimentation rate increased to 44 mm/1 hr. Repeated galactose tolerance tests showed an excretion of 0—1.7 g. The lipase value varied between 3 and 13. The excretion of urobilin ceased.

Biopsy of the liver showed degenerative parenchymatous changes and evidence of biliary stasis. Explorative operation and autopsy showed: Cancer of the common bile duct with occlusion.

The increased value for serum iron on the first examination was presumably due to deterioration of the liver parenchyma, which also gave rise to the high lipase values, and which was verified on biopsy.

The galactose tolerance test was performed on 7 of the patients, 5 of whom showed an excretion of 0—1.8 g, while 2 excreted more than 3 g.

The quinine-resistant lipase content of the serum was determined in 4 patients: 1 showed a value of 3, 1 a value of 8, and 2 gave values varying between 3 and 15.

Urine analysis showed evidence of complete occlusion of the bile passages in 2 patients (0 urobilin; + bilirubin). The remaining patients showed urobilinuria.

In 7 patients with *cholelithiasis* (verified by operation in 1, by roentgenography in 2) the serum iron concentration was determined altogether 8 times. In 5 of these patients the values were from 99 to 181 γ %, i. e., within normal limits; in 2 they were decreased.

The icterus index was slightly increased in 4 of these patients (9—24), markedly increased (52—68) in 3. The galactose tolerance test was performed on 5 patients, showing an excretion of 0—0.7 g in 3, 2.6 g in 1, and 6.8 g in 1.

The lipase value was increased in 1 patient.

The urobilin reaction was positive in 6 patients, negative in 1.

Discussion.

As the total results of the present examination of 50 patients suffering from lesions of the liver and bile passages, an increase in serum iron to over 200 γ % was found in 18 out of 26 patients (69 %) with acute hepatitis and in 1 out of 5 patients with cirrhosis

of the liver, whereas an increase in serum iron was seen in only 1 out of 19 patients with jaundice due to cancer or cholelithiasis.

These findings are quite in harmony with previous experiences (Table 1).

For comparison it may be mentioned that the galactose tolerance test gave an excretion of more than 3 g of galactose in the urine in 8 out of 19 patients with hepatitis, and in 3 out of 12 patients with cancer or cholelithiasis. An excretion between 2 and 3 g was found respectively in 6 patients and 1.

The cause of the rise in serum iron in patients suffering from hepatitis is not yet known precisely.

On the whole, the serum iron concentration may be assumed to depend on a number of more or less known factors: the absorption of iron from the digestive tract, storage in and mobilization from the iron depots, consumption of iron in the hemoglobin formation, liberation of iron in the decomposition of hemoglobin, and the still somewhat obscure iron metabolism of the cellular parenchyma.

We can rule out the possibility that the high values for serum iron in hepatitis might be due to an increased absorption of iron from the digestive canal. On peroral administration of soluble ferrous salts to patients with hepatitis Waldenström (12) and Vahlquist (11) found no increase in serum iron or, most often, a considerably smaller increase than observed in normal subjects.

Hemmeler (5) advanced the hypothesis that the high values for serum iron in hepatitis would result from a decreased excretion of iron with the bile, whereas in patients with mechanical jaundice other factors would assert themselves (infection, anemia) causing a decrease in serum iron. This hypothesis has to be refuted, however. As pointed out more thoroughly in a previous paper (2), it seems reasonable from more recent studies to assume that practically no iron is excreted with the excretions of the digestive tract.

So the cause of the increase in serum iron in hepatitis has to be looked for in the intermediate iron metabolism.

It seems more likely that the high values for serum iron in hepatitis are connected with the liberation of iron from the disintegrating iron-rich liver cells and with the simultaneous failure of the liver to absorb the iron liberated by the physiological decomposition of hemoglobin. On the other hand, it seems rather peculiar that the other iron depots of the organism — in particular, the

spleen and bone marrow — should not be able temporarily to take over the role of the liver as depot organ.

After intravenous injection of iron salts, Hemmeler (5) found that the rate with which the iron was removed from the blood stream in hepatic patients did not differ definitely from the normal. Nor did the intravenous injection of iron salts in two of the patients in the present work (Nos. 3 and 15) give any characteristic deviation from the normal. On the whole, it seems doubtful whether this method of examination meets the expectations it should fulfil theoretically, but these aspects will be dealt with in a subsequent paper.

It has to be recognized, I think, that the cause of the increase in serum iron in hepatitis cannot be pointed out clearly on the basis of our present knowledge.

As to the entirely practical question whether determination of the iron content of the serum is of any differential diagnostic importance in the examination of patients with diseases of the liver and bile passages, according to our experiences so far the conclusion will have to be as follows:

Serum iron values over 200 γ % have been found in 39 out of 75 patients with acute hepatitis (52 % — in previous investigations 43 %, in the writer's material 69 %) and in 2 out of 34 patients with cancer or cholelithiasis (6 %).

On examination of such patients the finding of a serum iron concentration exceeding 200 γ % constitutes a very weighty evidence of hepatitis, but these high values can be expected to turn up in only about one-half to two thirds of the patients with acute hepatitis — most often in the first weeks of the illness. So determination of serum iron may be of practical use only as a supplementary diagnostic adjuvant.

In conclusion it has to be added that increased values for serum iron may also be found in other affections, especially pernicious, aplastic and hemolytic anemia.

Summary.

1. The iron content of serum was found to be increased to over 200 γ % in 18 out of 26 patients suffering from acute hepatitis (69 %) and in 1 of 5 patients with cirrhosis of the liver, but only

in 1 out of 19 patients with jaundice due to cancer or cholelithiasis. These results are in good agreement with previous experiences.

2. Repeated determinations of the serum iron in hepatic patients showed great individual variations. The maximum was observed most often in the second week of illness.

No regular relation was found between the variations in serum iron, icterus index and lipase value.

3. The cause of the increase in the iron content of the serum in hepatitis is discussed. The high values cannot be due to changes in the exogenous iron metabolism, but are presumably attributable to the liberation of iron from the deteriorating iron-rich liver cells and a coincident failure of absorption by the liver of iron liberated by the physiological decomposition of hemoglobin.

4. In the examination of patients with lesions of the liver and bile passages, the finding of more than 200 γ % serum iron is a weighty evidence of the presence of hepatitis, but this sign is found only in about one half to two-thirds of the patients with acute hepatitis.

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Eine auf der Diazofarbe beruhende Methode zur quantitativen Bestimmung des aus Flüssigkeit extrahierten Bilirubins.

Von

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(Bei der Redaktion am 7. August 1942 eingegangen).

Im Jahre 1932 habe ich zusammen mit Leikola¹ eine Methode zur quantitativen Bestimmung des Bilirubins veröffentlicht, bei der das Bilirubin aus der zu prüfenden Flüssigkeit ausgezogen und mit Hilfe seiner eigenen gelben Farbe bestimmt wird. 1936² verbesserte ich die Methode insofern, als die störenden sogenannten Lipochromfarbstoffe im Serum unter Benutzung der Eigenschaft des Bilirubins, wasserlösliche Alkalisalze zu bilden, entfernt werden konnten. Zugleich machte ich die Methode für das Stufenphotometer anwendbar.

Auch in ihrer letzteren Form weist die Methode noch einen Punkt auf, der der Präzisierung bedarf. Wie ich schon erwähnte, wird bei ihr die quantitative Bestimmung durch Messung der eigenen Farbe des Bilirubins ausgeführt. Es ist jedoch bekannt, dass sich das Bilirubin in bezug auf seine Farbe, unter anderem bei der Oxydation, leicht verändert, und infolgedessen können wir nicht sicher sein, dass die Farbe in den nach meiner Methode hergestellten Extrakten stets dieselbe bleibt. Die Farbe des Bilirubins können

¹ Acta med. scandinav. Vol. LXXVIII, Fasc. I, 1932.

² Acta med. scandinav. Vol. LXXXIX, Fasc. V, 1936.

wir genau mit Hilfe seiner Absorptionskurve bestimmen. Wenn die Kurven sich in den auf gleiche Weise hergestellten Proben immer decken, dürfen wir annehmen, dass das Bilirubin unter diesen Verhältnissen mit gleicher Farbe auftritt und dass zur Anwendung gekommene Verfahren zur Bestimmung des Bilirubins exakt gewesen ist.

Beim Ausziehen von Serum mit Chloroform löst sich in diesem nur das reine Bilirubin und keine anderen Farbstoffe (vgl. meine früheren Veröffentlichungen). Beim Studium der Absorptionskurve des aus Serum von Kindern mit Icterus neonatorum in Chloroform löslichen Bilirubins konnte Ylppö¹ feststellen, dass die Farbe des Bilirubins bei ihnen immer dieselbe ist. Ich habe eine ähnliche Untersuchung in 25 verschiedenartigen Ikterusfällen ausgeführt und bin zu dem gleichen Ergebnis gelangt. Die Absorptionskurve des aus dem Serum unmittelbar in Chloroform löslichen Bilirubins ist symmetrisch mit der Kurve, die man für Bilirubin erhält, das aus Gallensteinen nach der Küsterschen Methode hergestellt ist.² Dieses Bilirubins bediente ich mich, als ich eine Vergleichskurve für die Bestimmung des Bilirubins auf Grund seiner eigenen Farbe mit dem Stufenphotometer berechnete. Bedenken wir ferner, dass die Farbe des Bilirubins sich bei der Oxydation leicht verändert und dass damit, wie ich früher zusammen mit Leikola³ gezeigt habe, in den Absorptionskurven der Farben grosse Veränderungen stattfinden, so darf ich wohl annehmen, dass bei der Bestimmung des *reinen Bilirubins* nach der ursprünglich von mir und Leikola angegebenen und später von mir modifizierten Methode die Farbenvariationen des Bilirubins nicht auf die Zuverlässigkeit der Ergebnisse einwirken.

Können wir nun bei der Bestimmung des Gesamtbilirubins nach meiner Methode Beweise für die Einheitlichkeit der Farbe des Bilirubins finden? Bei dieser Methode lösen sich aus dem Serum in das Chloroform in grösserer oder geringerer Menge sogenannte Lipochromfarbstoffe, die die Verwendung einer Absorptionskurve für diesen Zweck unmöglich machen. Ziehen wir aber in Betracht, dass das Bilirubin aus dem Serum immer bei derselben Azidität extrahiert wird, dass die Farbe stets in dem

¹ Z. Kinderheilk. 1913.

² Skandin. Arch. f. Physiologie. Bd. 54, H. 3—4. 1928.

³ Skandin. Arch. f. Physiologie. Bd. 55, 1929.

gleichen Lösungsmittel bestimmt wird und die Farbe des Bilirubins bei der Bestimmung des reinen Bilirubins als unveränderlich erwiesen werden konnte, so ist es wahrscheinlich, dass auch bei der Bestimmung des Gesamtbilirubins in verschiedenen Fällen keine grösseren Farbenvariationen vorhanden sind; volle Sicherheit lässt sich jedoch in dieser Hinsicht vorläufig nicht erzielen.

Um meine Methode auch in dieser Beziehung sicherzustellen, bin ich dazu übergegangen, als Mass des Bilirubins nach der Extraktion seine Diazofarbe zu benutzen, die den allermeisten Methoden zur quantitativen Bestimmung des Bilirubins zugrunde liegt und die nach den früheren Forschern eine stets gleich gefärbte und beständige Farbenverbindung ist. Die Bestimmung der Diazofarbe erfolgt in einem lichtstärkeren Teil des Spektrums als die der eigenen gelben Farbe des Bilirubins und ist daher in dieser Hinsicht vorteilhafter. Bei der von mir entworfenen Methode zur quantitativen Bestimmung des Bilirubins wird die Diazoreaktion in dem aus Serum erhaltenen Chloroformauszug und nicht, wie bei allen früheren Verfahren, im Serum selbst angestellt. Schon früher habe ich mit Leikola¹ konstatiert, dass die Reaktion am besten mit folgenden Bestandteilen ausgeführt wird: Chloroformlösung 0.5 cm³, Diazomischung ebenfalls 0.5 cm³ und Alkohol 1.3 cm³. In einer früheren Veröffentlichung habe ich gezeigt², dass im Serum oft ein farbloses, Diazoreaktion gebendes Chromogen festzustellen ist, das sich am besten in Benzol, aber auch in Chloroform löst. Das Chromogen bleibt in der Lösung, wenn wir daraus mit einer Alkalimischung das Bilirubin entfernen. Das ist bei der unten beschriebenen Bestimmungsmethode berücksichtigt, die übrigens auf dieselbe Weise durchgeführt wird, wie ich die Bestimmung des reinen Bilirubins und des Gesamtbilirubins bei Anwendung der eigenen Farbe des Bilirubins als Massstab dargelegt habe. Ich verweise diesbezüglich auf meine frühere bereits erwähnte Veröffentlichung. Ich habe den Bilirubingehalt der nach der Extraktion des Bilirubins zurückgebliebenen Flüssigkeit von neuem untersucht und konnte feststellen, dass hier alle Reaktionen des Bilirubins negativ sind, die Diazoreaktion auch nach Koffeinzusatz.

¹ Acta med. scandin. Vol. LXXVI, Fasc. IV—VI, 1931.

² Acta med. scandin. Vol. LXXXIX, Fasc. V, 1936.

Nach meiner neuen Methode findet die quantitative Bestimmung des reinen Bilirubins und des Gesamtbilirubins folgendermassen statt:

Bestimmung des reinen Bilirubins:

4 cm³ Serum

8 cm³ Chloroform wird 5 Min. kräftig im Schüttelapparat geschüttelt.

Es wird 5 Min. zentrifugiert.

1 cm³ klare Chloroformlösung wird in das Reagensglas A und 2 cm³ in das Reagensglas B pipettiert.

Reagensglas A

1 cm³ Chloroformlösung

1 cm³ Diazomischung (Sulfanillösung 10 cm³ und 0.5 % Natriumnitrit 0.25 cm³).

3 cm³ 95 % Alkohol, wird zugesetzt und bleibt 10 Min. stehen.

Die Farbe wird mit dem Stufenphotometer bestimmt, 10 mm-Küvette, Filter S. 57. Aus der Heilmeyerschen ¹ Tabelle (Tabelle I) wird die entsprechende Bilirubinmenge abgelesen und die Zahl mit 10 multipliziert.

Reagensglas B

2 cm³ Chloroformlösung

4 cm³ Alkohol-Laugelösung (1 Teil 95 % Alkohol und 4 Teile 10 % Natr.-Lauge), wird 5 Min. geschüttelt und zentrifugiert.

Weiter wie bei Reagensglas A

A—B = reines Bilirubin in mg %.

Bestimmung des Gesamtbilirubins:

4 cm³ Serum

8 cm³ Eisessig

16 cm³ 10 % Trichloressigsäure, wird 5 Min. kräftig im Schüttelapparat geschüttelt. 5 Min. zentrifugiert.

1 cm³ klare Chloroformlösung wird in das Reagensglas A und 2 cm³ in das Reagensglas B pipettiert.

Weiter wie bei der Bestimmung des reinen Bilirubins

A—B = Gesamtbilirubin in mg %.

¹ Carl Urbach: Stufenphotometrische Absorptionsbestimmungen in der medizinischen Chemie. Emil Haim & Co., Wien-Leipzig 1932. S. 102—105, Tabelle XXI.

Wollen wir im Serum eine vollständige Bestimmung des Bilirubins ausführen, so brauchen wir dazu 8 cm³ Serum, das wir aus etwa 20 cm³ Blut bekommen. In den meisten Fällen können wir uns jedoch mit einer Bestimmung des Gesamtbilirubins begnügen, wobei wir mit einer um die Hälfte kleineren Blutmenge auskommen. Die Bestimmung des reinen Bilirubins ist gleichwohl in gewissen Fällen, vor allem bei der Feststellung von hämolytischem Ikterus, von Wichtigkeit (vgl. meine frühere Veröffentlichung, *Acta med. scandin.* Vol. XCVIII, Fasc. III, 1939).

Tabelle I veranschaulicht die in 24 verschiedenen Ikterusfällen ausgeführte Bilirubinbestimmung nach der oben beschriebenen Methode. In dieselbe Tabelle sind auch die nach meiner früheren Methode gefundenen entsprechenden Mengen des Bilirubins aufgenommen. Vor allem sind in der Tabelle zwei Umstände zu beachten. Die Werte im Reagensglas B bringen die Intensität der Diazofarbe zum Ausdruck, nachdem das Bilirubin durch die Alkalimischung aus der Chloroformlösung entfernt worden ist. Vor der Ausführung der Diazoreaktion ist die Chloroformlösung bei der Bestimmung des freien Bilirubins regelmässig farblos, bei der Bestimmung des Gesamtbilirubins dagegen infolge der Lipochromfarbstoffe mehr oder weniger gelb. In den meisten Fällen enthält das Serum eine Diazoreaktion gebende Substanz, die kein Bilirubin ist, in verhältnismässig geringer Menge, und zwar beträgt ihr Wert höchstens 10 % von der Menge des Bilirubins, aber häufig steigt sie auf 25 % und sogar darüber (die Fälle 2, 3, 11, 14 und 23 bei freiem Bilirubin und Fall 2 bei Gesamtbilirubin). Wollen wir uns mit Werten begnügen, bei denen der Fehler 10 % im allgemeinen nicht überschreitet, so können wir bei der Bestimmung des Gesamtbilirubins das Reagensglas B weglassen, wobei wir mit einer kleinen Blutmenge auskommen und die Untersuchung sich schnell ausführen lässt.

Aus der Tabelle ersehen wir ferner, dass die mit der jetzt vorgelegten und die mit der früheren Methode zur Bestimmung des Bilirubins gefundenen Werte in den allermeisten Fällen übereinstimmen. Für das freie Bilirubin erhält man beinahe die gleichen Werte, die Mengen des Gesamtbilirubins sind im allgemeinen bei meiner früheren Methode etwas niedriger als die durch die Diazofarbe festgestellten. Die erwähnten Befunde sind dazu angetan,

Tabelle 1.

D % = Trommelablesewert. A % = Bilirubin in mg %.

D %	A %	D %	A %	D %	A %
8.0	1.012	8.1	1.007	8.2	1.002
8.3	0.997	8.4	0.992	8.5	0.987
8.6	0.983	8.7	0.978	8.8	0.973
8.9	0.969	9.0	0.965	9.1	0.960
9.2	0.955	9.3	0.951	9.4	0.947
9.5	0.943	9.6	0.939	9.7	0.934
9.8	0.930	9.9	0.926	10.0	0.922
10.1	0.918	10.2	0.914	10.3	0.910
10.4	0.907	10.5	0.903	10.6	0.899
10.7	0.895	10.8	0.891	10.9	0.888
11.0	0.884	11.1	0.880	11.2	0.877
11.3	0.873	11.4	0.870	11.5	0.866
11.6	0.863	11.7	0.859	11.8	0.856
11.9	0.853	12.0	0.849	12.1	0.846
12.2	0.843	12.3	0.839	12.4	0.836
12.5	0.833	12.6	0.830	12.7	0.826
12.8	0.823	12.9	0.820	13.0	0.817
13.1	0.814	13.2	0.811	13.3	0.808
13.4	0.805	13.5	0.802	13.6	0.799
13.7	0.796	13.8	0.793	13.9	0.790
14.0	0.787	14.1	0.785	14.2	0.782
14.3	0.779	14.4	0.776	14.5	0.773
14.6	0.771	14.7	0.768	14.8	0.765
14.9	0.762	15.0	0.760	15.1	0.757
15.2	0.755	15.3	0.752	15.4	0.749
15.5	0.747	15.6	0.744	15.7	0.742
15.8	0.739	15.9	0.736	16.0	0.734
16.1	0.731	16.2	0.729	16.3	0.726
16.4	0.724	16.5	0.722	16.6	0.719
16.7	0.717	16.8	0.714	16.9	0.712
17.0	0.710	17.1	0.707	17.2	0.705
17.3	0.703	17.4	0.700	17.5	0.698
17.6	0.696	17.7	0.693	17.8	0.691
17.9	0.689	18.0	0.687	18.1	0.685
18.2	0.682	18.3	0.680	18.4	0.678
18.5	0.676	18.6	0.674	18.7	0.671
18.8	0.669	18.9	0.667	19.0	0.665
19.1	0.663	19.2	0.661	19.3	0.659
19.4	0.657	19.5	0.655	19.6	0.653
19.7	0.651	19.8	0.649	19.9	0.647

(Tabelle 1 Forts.)

D %	A %	D %	A %	D %	A %
20.0	0.615	20.1	0.613	20.2	0.611
20.4	0.637	20.6	0.633	20.8	0.629
21.0	0.625	21.2	0.621	21.4	0.617
21.6	0.614	21.8	0.610	22.0	0.606
22.2	0.603	22.4	0.599	22.6	0.596
22.8	0.592	23.0	0.589	23.2	0.585
23.4	0.582	23.6	0.578	23.8	0.575
24.0	0.572	24.2	0.568	24.4	0.565
24.6	0.562	24.8	0.558	25.0	0.555
25.2	0.552	25.4	0.549	25.6	0.546
25.8	0.543	26.0	0.540	26.2	0.536
26.4	0.533	26.6	0.530	26.8	0.527
27.0	0.524	27.2	0.521	27.4	0.518
27.6	0.516	27.8	0.513	28.0	0.510
28.2	0.507	28.4	0.504	28.6	0.501
28.8	0.499	29.0	0.496	29.2	0.493
29.4	0.490	29.6	0.488	29.8	0.485
30.0	0.482	30.2	0.480	30.4	0.477
30.6	0.474	30.8	0.472	31.0	0.469
31.2	0.467	31.4	0.464	31.6	0.461
31.8	0.459	32.0	0.456	32.2	0.451
32.4	0.451	32.6	0.449	32.8	0.447
33.0	0.444	33.2	0.442	33.4	0.439
33.6	0.437	33.8	0.435	34.0	0.432
34.2	0.430	34.4	0.427	34.6	0.425
34.8	0.423	35.0	0.421	35.2	0.418
35.4	0.416	35.6	0.414	35.8	0.411
36.0	0.409	36.2	0.407	36.4	0.405
36.6	0.403	36.8	0.400	37.0	0.398
37.2	0.396	37.4	0.394	37.6	0.392
37.8	0.390	38.0	0.388	38.2	0.386
38.4	0.383	38.6	0.381	38.8	0.379
39.0	0.377	39.2	0.375	39.4	0.373
39.6	0.371	39.8	0.369	40.0	0.367
40.5	0.362	41.0	0.357	41.5	0.352
42.0	0.348	42.5	0.343	43.0	0.338
43.5	0.333	44.0	0.329	44.5	0.324
45.0	0.320	45.5	0.315	46.0	0.311
46.5	0.307	47.0	0.302	47.5	0.298
48.0	0.294	48.5	0.290	49.0	0.286
49.5	0.282	50.0	0.278	50.5	0.274

(Tabelle 1 Forts.)

D %	A %	D %	A %	D %	A %
51.0	0.270	51.5	0.265	52.0	0.262
52.5	0.258	53.0	0.254	53.5	0.251
54.0	0.247	54.5	0.243	55.0	0.239
55.5	0.236	56.0	0.232	56.5	0.229
57.0	0.225	57.5	0.222	58.0	0.218
58.5	0.215	59.0	0.211	59.5	0.208
60.0	0.205	61.0	0.198	62.0	0.191
63.0	0.185	64.0	0.179	65.0	0.173
66.0	0.166	67.0	0.160	68.0	0.154
69.0	0.149	70.0	0.143	71.0	0.137
72.0	0.132	73.0	0.126	74.0	0.121
75.0	0.115	76.0	0.110	77.0	0.105
78.0	0.099	79.0	0.094	80.0	0.089
81.0	0.084	82.0	0.079	83.0	0.075
84.0	0.070	85.0	0.065	86.0	0.060
87.0	0.056	88.0	0.051	89.0	0.047
90.0	0.042	91.0	0.038	92.0	0.033
93.0	0.029	94.0	0.025	95.0	0.020
96.0	0.016	97.0	0.012	98.0	0.008
99.0	0.004	100.0	0.000.		

die Zuverlässigkeit der angewandten Methoden in bedeutendem Masse zu erhöhen.

Von der Diazoreaktion ist bei der Bestimmung des Bilirubins im Serum bereits fast ein Vierteljahrhundert Gebrauch gemacht worden. Seitdem Hijmans van den Berg¹ seine Originalmethode mitteilte, ist versucht worden, sie auf verschiedene Weise zu verbessern. Allen Methoden ist jedoch gemein, dass die Reaktion im Serum selbst entweder als solchem oder unter Zusatz gewisser Stoffe, wie Alkohol (Hijmans van den Berg) oder Koffein (Enriques²), gemacht wird.

Wenn wir das oben vorgeführte Verfahren zur quantitativen Bestimmung des Bilirubins und die früheren Methoden, bei denen die Diazoreaktion angewandt wird, miteinander vergleichen, so finden wir, dass sie sich vor allem darin unterscheiden, dass bei

¹ Der Gallenfarbstoff im Blute. Leipzig 1918.

² Revista crit. di clin. med. Nr. 23 und 24. 1924.

allen früher gebräuchlichen Bestimmungsmethoden das Bilirubin im Serum selbst bestimmt wird, während es bei meiner Methode zuerst aus dem Serum ausgezogen wird. Meine Methode kann sich mithin auf mehrere verschiedene Eigenschaften des Bilirubins gründen. Erstens wird bei ihr berücksichtigt, dass sich das Bilirubin aus Wasserlösungen von mehr als pH 5 vollständig in Chloroform löst, zweitens die Fähigkeit der Bilirubinsäure, wasserlösliche Alkalisalze zu bilden, drittens die Diazofarbe des Bilirubins und bei meiner früheren Methode seine eigene Farbe. Ausserdem beobachtet man bei der Methode das früher von mir im Serum konstatierte farblose, Diazoreaktion gebende Chromogen, das in seinen Eigenschaften durchaus von dem Bilirubin abweicht, und die Lipochromfarbstoffe des Serums. Alle früheren Methoden bauen dagegen ausschliesslich auf der Diazofarbe des Bilirubins, und das von mir erwähnte Chromogen ist bei ihnen nicht beobachtet worden. Wird dem Serum noch eine Eiweiss fällende Substanz, wie Alkohol, zugesetzt, so fällt mit ihr eine erhebliche Menge Bilirubin aus, wie von mehreren früheren Forschern und auch von mir selbst in einer früheren Veröffentlichung zusammen mit Leikola¹ gezeigt worden ist.

Vergleichshalber habe ich noch Parallelbestimmungen nach der in letzter Zeit viel empfohlenen Methode von Jendrassik-Cleghorn², bei der dem Serum vor der Diazoreaktion Koffein-Natriumazetatlösung zugesetzt wird, und nach meiner eigenen oben beschriebenen Methode ausgeführt.

Ich führe zuerst die Ergebnisse in Ikterusfällen an, in denen die direkte Diazoreaktion im Blute negativ ist und kein Bilirubin in den Harn übergeht. An Fällen, zu denen u. a. hämolytischer Ikterus gehört, enthält mein Material wegen ihrer Seltenheit nur einige. Die Regel war, dass die mit der Jendrassik-Cleghornschen Methode festgestellten Werte kleiner, ja viel niedriger als die mit meiner obigen Methode gefundenen sind. Als Beispiel sei folgender Fall erwähnt: Exstinktionskoeffizient der Farbe des Serums 3.8, Bilirubin nach meiner Methode 2.7 mg % und nach Jendrassik-Cleghorn 0.55 mg %; trotzdem sich auch der Farbwert des Serums etwa vervierfacht hat, erhalten wir also mit der letzterwähnten

¹ Acta med. scandin. Vol. LXXVIII, Fasc. 1. 1932.

² Biochem. Z. I, 1 und 239, 5—6, 483.

Methode einen normalen Bilirubinwert. Als ich in einer früheren Veröffentlichung¹ meine ältere Methode mit der Heilmeyerschen verglich, bei der die Diazoreaktion unmittelbar im Serum nach Alkoholzusatz gemacht wird, bekam ich in Ikterusfällen entsprechender Art dasselbe Resultat. Die Ergebnisse sind verständlich, wenn wir bedenken, dass die Diazoreaktion in diesen Fällen im Serum negativ ist und der Koffein- oder Alkoholzusatz wahrscheinlich nicht zu bewirken vermag, dass die ganze Bilirubinsmenge mit einer Diazoreaktion reagiert.

Zu einem ganz entgegengesetzten Resultat gelangen wir, wenn Galle in das Blut gedrungen ist, die direkte Diazoreaktion ist positiv, und es tritt Bilirubin im Harn auf. Bei der Jendrassik-Cleghornschen Methode sind die Werte dann regelmässig höher als bei meiner Methode, ja sie erreichen das Drei- bis Vierfache. Dasselbe Ergebnis stellt sich bei den Bestimmungen des Bilirubins in der Galle ein. Wie ich schon in der erwähnten Veröffentlichung gezeigt habe, erhält man auch in dieser Ikterusgruppe mit der Heilmeyerschen Methode niedrigere Werte als mit meinem Verfahren, doch kommen dieselben einander nahe. Worin liegt nun die Ursache dazu, dass Zusatz von Koffein-Natriumazetat die Intensität der Diazofarbe vervielfacht? In dieser Hinsicht kann ich keine sichere Erklärung geben, jedoch weise ich darauf hin, dass ich gezeigt zu haben glaube, dass im Serum sogar grosse Mengen eines farblosen, Diazoreaktion gebenden Stoffes auftreten können, der kein Bilirubin ist.

Zusammenfassung.

Im Jahre 1936 hat der Verfasser in dieser Zeitschrift (Vol. LXXXIX, Fasc. V) eine Methode zur quantitativen Bestimmung des Bilirubins mitgeteilt, bei der das Bilirubin aus der zu prüfenden Flüssigkeit ausgezogen und mit Hilfe seiner eigenen Farbe bestimmt wird. Nunmehr ist die Methode dahin abgeändert worden, dass als Massstab die Diazofarbe des Bilirubins statt seiner eigene Farbe zur Verwendung kommt. Die Diazoreaktion wird nach der Extraktion in einer Chloroform-Alkoholmischung ausgeführt. Die mit

¹ Acta med. scandin. Vol. LXXXIX, Fasc. V. 1936.

der zuletzt angegebenen und die mit der früheren Methode gefundenen Bilirubinwerte stimmen in den allermeisten Fällen gut überein.

Vergleicht man die neue mit den früheren Methoden, bei denen die Diazoreaktion unmittelbar im Serum angestellt wird, so kann man konstatieren, dass die gefundenen Werte sogar stark voneinander abweichen. Die Unterschiede konnten teils erklärt werden, teils liess sich wahrscheinlich machen, dass sie auf Fehlern in den früheren Bestimmungsmethoden beruhen.

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On the Clot-retraction of the blood.

By

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(Submitted for publication August 7, 1942).

It has long been known that coagulated blood after a space of time separates into clot (*cruor sanguinis*) and serum. This phenomenon, which is usually called the retraction of the coagulum, is undoubtedly of great biologic significance, because a thrombus that has closed a defect in an injured blood vessel will thus in short time become firm and solid and thereby ensure hemostasis.

Under certain pathologic conditions the blood lacks, however, this power to retract. This was already observed in 1822 by two Edinburgh physicians, Duncan (1) and Johnstone (6), who, strange to say, had used venesection as treatment for some patients who, to judge from the description, must have had thrombopenic purpura. But not until many years after was it shown, by Hayem (5), that the process of retraction depends chiefly on the blood platelets. Thus, reduced retraction is found both in diseases where the platelet count is diminished and in cases where the thrombocytes are altered qualitatively, as in Glanzmann's hereditary hemorrhagic thromboasthenia.

Many workers have therefore been interested in studying this retraction power of the coagulated blood, and several methods have been employed in this study. The one most commonly used is Fonio's (2), which consists in letting 1 cm³ of blood coagulate in a special glass tube with an inside diameter of 5 mm and then letting it stand for twenty-four hours at room temperature. At the end of

that time the distance from the upper level of the clot to the surface of the supernatant serum (normally 6—8 millimeters) is measured. This is, of course, a very crude method (Fig. 1). A more acceptable one is Macfarlane's (9) which consists in pipetting 2 cm³ of blood into a graduated centrifuge tube, in the middle of which

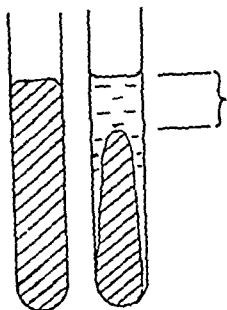


Fig. 1. — Determination of the retraction by Fornio's method.

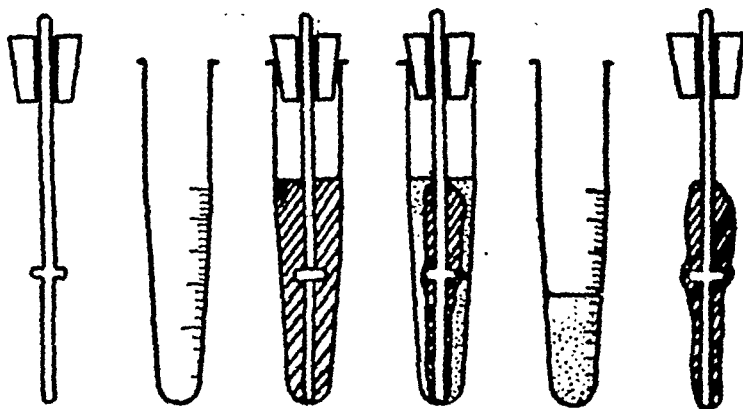


Fig. 2. — Diagram showing glass rod, cork, and graduated centrifuge tube, and method of removing clot to measure serum expressed.

is placed a rod with a small «button» expansion at the lower end. After the tube has been standing in water bath for 1 hour at 37° C the coagulum will have settled on this rod, which is then withdrawn. The expressed fluid will remain in the tube, and its volume, which is a direct measure for the retraction, may be read off on the graduated scale (Fig. 2).

Also MacFarlane's method is open to some objections, though. In the first place, the coagulum as a rule adheres not only to the rod, but also to the wall of the tube, and therefore becomes torn to pieces when the rod is withdrawn. I have tried to avoid this by coating the inside of the tube with paraffin, but without great result. Another fault of the method is in my opinion the use of

blood. The normal retraction is namely 50 per cent of the quantity of blood, which means that the volume of the clot is likewise 50 per cent. But four-fifths of this is derived from the blood corpuscles. It is therefore evident that the result in a very great measure must depend on the cell-volume percentage, and it therefore becomes necessary to introduce a correction for this. Still another inconvenience is that the expressed fluid consists not only of serum, but also of blood corpuscles. Thus I found in one experiment with 2 cm³ of citrated blood and 0.5 cm³ of CaCl₂ solution that of 1.6 cm³ of fluid expressed 0.3 cm³ were erythrocytes.

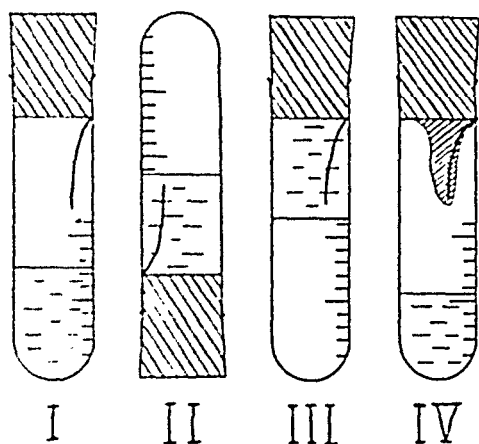


Fig. 3. — Determination of the retraction by the Author's method.

It is therefore obviously better to use plasma instead of blood, especially if one wishes to study the process of retraction from a biochemical point of view. For my experiments I used citrated blood produced by adding one part of a 3.7 per cent sodium citrate solution to four parts of blood. The blood was taken in the morning, and by afternoon the corpuscles would then as a rule have sunk to the bottom, so that a sufficient quantity of plasma could be pipetted off. The procedure was then as follows.

Two cubic centimeters of citrated plasma were pipetted into a graduated test tube with an inside diameter of 12 mm (a so-called Oluf Thomsen tube), which had beforehand been paraffined on the inside by sluicing with a saturated solution of paraffin in ether. The tube was then allowed to stand for a couple of minutes in water bath at 37° C, whereupon 0.5 cm³ of a 1.5 per cent solution of CaCl₂ in water was added and the tube closed with a tight-fitting

india rubber cork after a small bit of gaze, 15×20 mm, had been placed inside it in such a manner that a snip was held fast between the tube and the cork. After the contents had been thoroughly mixed, the tube was placed, inverted, in the incubator at 37° C (see Fig. 3). After 10 to 15 minutes, when the plasma had coagulated, it was again turned right side up and the clot would now have settled up by the cork, especially due to its adhering to the

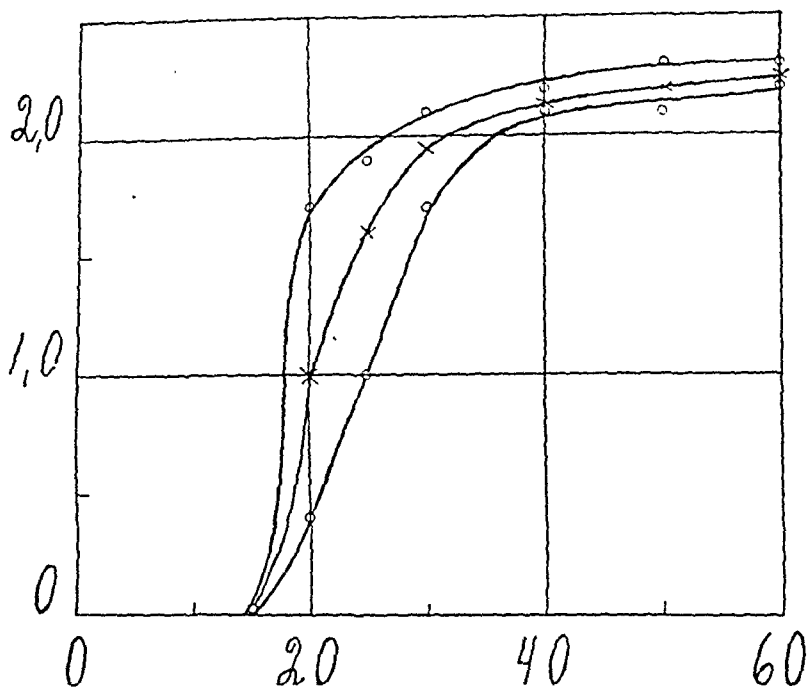


Fig. 4. — *Abscissa*: Time, in minutes. *Ordinate*: the retraction measured in cubic centimeters.

gaze, the presence of which had the further advantage that it furthered the coagulation, which otherwise was slow in the paraffined tube.

Some time after the coagulation had taken place, the retraction would begin, and the expressed serum would collect at the bottom of the tube. Every 5 minutes it was noted down how much had collected; if any drops kept adhering to the clot a tap on the tube would cause them to flow down. In this manner a curve could be plotted which showed the dependence of the retraction upon the time. The curves are of a very uniform, characteristic appearance, but unfortunately the investigations are not marked by any great exactitude. Fig. 4 shows the results of ten experiments made with

Table I.

The effect of varying amounts of calcium chloride on the retraction.

Percentage of calcium chloride in the citrated plasma.	Time required for the expression of 2 cm ³ of serum (minutes)
0.2	58
0.3	44
0.4	45
0.5	50
0.6	62

the same plasma; for the sake of readier survey only the highest and the lowest curve and the one representing the mean values are traced in. It will be seen that as long as the retraction is only beginning there are great variations between them; thus after twenty minutes the amount of serum expressed was in one case 0.4 cm³, in another 1.7 cm³. One reason of this is that the clot in spite of the paraffin adheres to the wall of the tube, which may hinder the retraction temporarily. Often, too, a not inconsiderable quantity of expressed serum may be seen to be enclosed for a short time between the tube wall and the clot. When the latter has once become loosened it will as a rule rapidly contract, and as a result the curves will always end by running together. It was therefore found that even when the curves in the beginning lay widely separated, the time until the retraction had set in almost completely did not vary very much. Instead of using the volume of serum formed within a certain time as measure for the retraction of the clot, I have therefore preferred to use as measure the time required for the formation of 2 cm³ of serum. Thus, the mean for the ten experiments just mentioned proved to be 32 minutes, with a standard deviation of 4.

With the method here described I was able to study the influence of diverse factors on the retraction, in the first place that of the calcium concentration. The results of this study are shown in Table I, from which it will be seen that the retraction is greatest when the mixture contains 0.3 to 0.4 per cent of calcium chloride, while higher and lower concentrations give less retraction.

Next, I obtained by centrifuging a series of plasma samples, each with different content of thrombocytes. Experiments with

Table II.

The effect of varying platelet count on the retraction.

Centrifuging time at 3,500 rev./min. (minutes)	Number of platelets per mm ³	Amount of serum expressed in 60 min- utes (cm ³)	Clotting time (minutes).
0	290,000	2.2	3 $\frac{1}{4}$
5	225,000	2.2	3 $\frac{1}{4}$
10	138,000	1.8	3 $\frac{3}{4}$
20	71,000	1.3	4 $\frac{1}{4}$
30	26,000	0.4	5 $\frac{1}{2}$
60	5,000	0.0	6 $\frac{1}{2}$

Table III.

The effect of varying platelet count on the retraction.

Number of platelets per mm ³	Time required for the expression of 2 cm ³ of serum (minutes)	Clotting-time (minutes)
356,000	30	2 $\frac{3}{4}$
213,000	45	4 $\frac{1}{2}$
112,000	60	5
34,000	105	6 $\frac{1}{2}$
5,000	233	8

these showed that the retraction depended on the number of platelets, and that it diminished in a particularly marked degree when the thrombocyte count in citrated plasma fell below 150,000. If we assume that the addition of citrate does not in any considerable degree alter the cell volume, the number of platelets in whole blood and in the native plasma may, on the basis of the platelet count in the citrated plasma, be calculated by the following formulae:

$$\frac{\text{Plasma volume per cent} + 25}{100} \times \text{citrated plasma count} = \text{blood count};$$

$$\frac{\text{Blood count} \times 100}{\text{Plasma volume per cent}} = \text{plasma count}.$$

The results of these experiments are shown in Tables II and III.

If plasma is left standing at 37° C its power to retract becomes considerably reduced and ceases entirely in the course of twenty-four hours, presumably because the platelets are destroyed by standing; but at the same time its coagulability, as said else-

Table IV.

The effect of standing at 37° C. and at room temperature (21° C.) on the coagulability of the plasma and its power to retract.

Number of hours left standing	Time required for the expression of 2 cm ³ of serum (minutes)		Clotting time (minutes)	
	at 37°	at 21°	at 37°	at 21°
0	30	30	6	6
4	48	—	1 $\frac{3}{4}$	—
8	58	—	1 $\frac{1}{2}$	2 $\frac{3}{4}$
24	indefinite	36	1 $\frac{1}{2}$	3 $\frac{1}{4}$

where (8), increases (see Table IV). Strange to say, the platelet count remains nearly unaltered, even after twenty-four hours.

These experiments, which confirm the findings of previous investigators (3, 10, 11), show that the platelets play a considerable rôle for the retraction. But it is not their thrombokinase that has any influence in that respect, because precisely under those conditions (the standing at 37° C) the retraction diminishes when the coagulability increases, and, as shown before (8), this is due to the thrombokinase in the platelets being set free and passing over into the plasma. This was further shown by an experiment with plasma that had been centrifuged for one hour at 3,500 revolutions per minute and was in consequence practically platelet-free. It had therefore no power to retract nor did it do so even when thrombokinase from brain tissue was added, which on the other hand considerably hastened the coagulation.

The plasma's power to retract is only slightly altered by twenty-four hours' stand at room temperature or in refrigerator; but it must be shaken very thoroughly, as otherwise the platelets will clump together and sink to the bottom.

Several investigators have examined the clot in various ways under the microscope in order to study its structure (12). Specially interesting are Tocantins's (13) ultramicroscopic studies of the clotting of hemophilic plasma in moist chamber. He found that the first stage consists in the formation of fine fibrin threads, then the platelets clump together in the angles between these threads, and then the retraction begins. Figs. 5 and 6 show photomicrographs of sections of clot from an ordinary plasma and from a plasma that

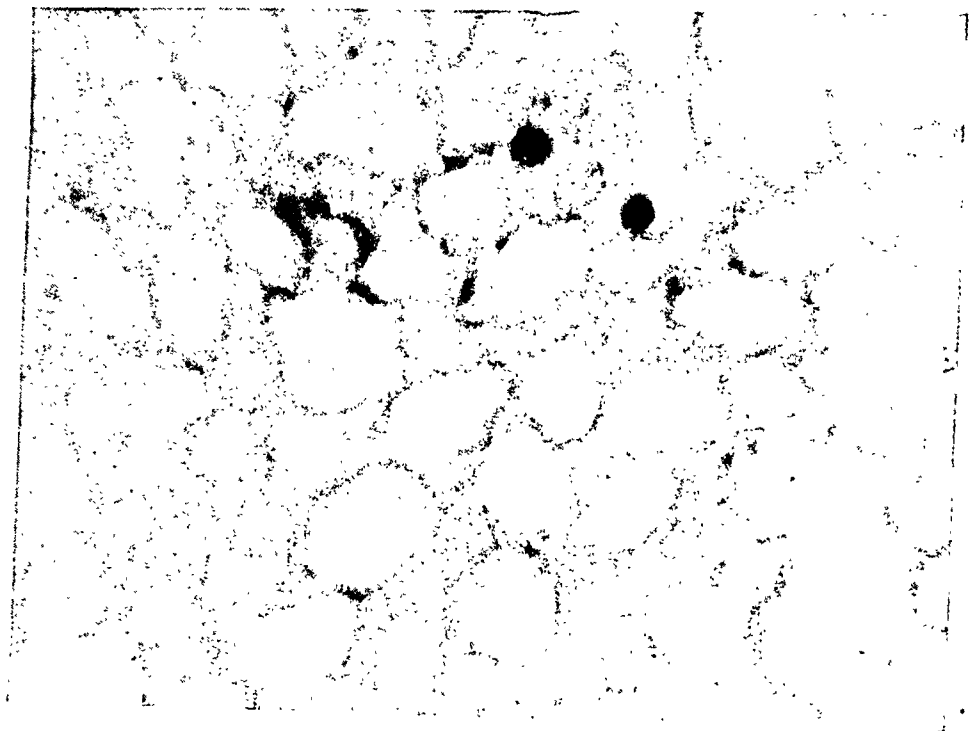


Fig. 5. — Photomicrograph (oil-immersion) of fibrin clot in which there has been considerable retraction.

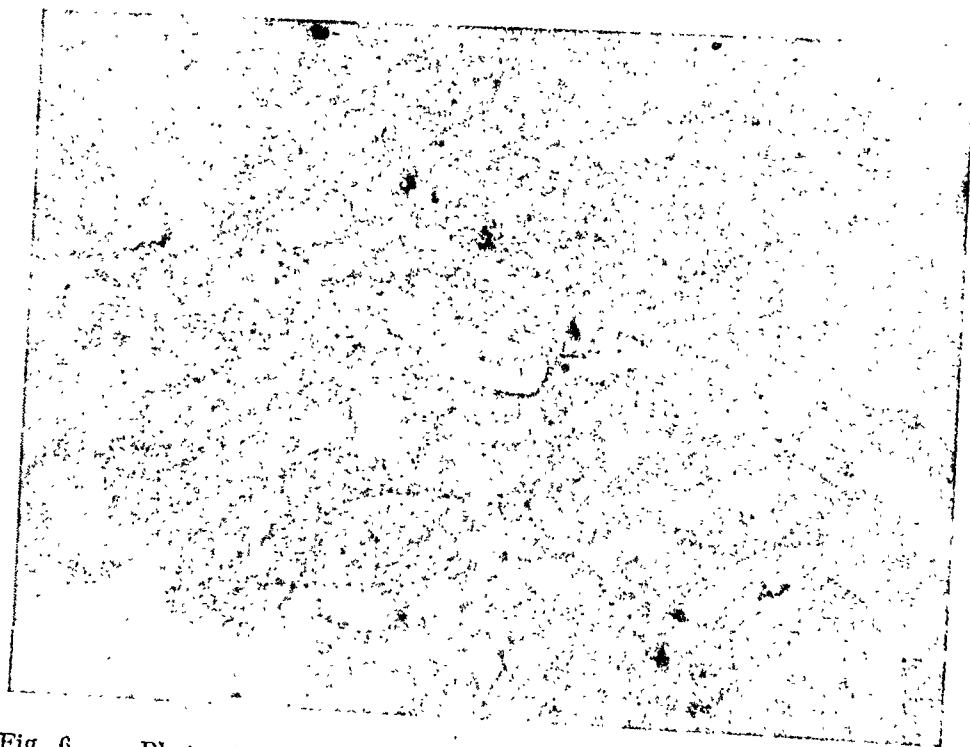


Fig. 6. — Photomicrograph (oil-immersion) of fibrin clot in which there has been no retraction.

Table V.

The effect of the fibrinogen concentration on the retraction. (In each of the experiments, 0.5 cm³ of 2 per cent calcium chloride and 0.2 cm³ of a suspension of platelets in plasma were added to the mixtures of plasma and serum stated in the Table).

Hard centrifuged citrated plasma (cm ³)	Citrated serum (cm ³)	Percentage of fibrinogen in the mixture	Time required for the expression of 2 cm ³ of serum (minutes)
2.0	0.0	0.33	56
1.0	1.0	0.18	44
0.5	1.5	0.11	28

has been made practically platelet-free by centrifuging. In the first, where there has been marked retraction, the fibrin threads are lying roughly bundled together, forming a network with large meshes; in the second, where there has been no retraction, the fine threads lie isolated, without forming any distinct structure.

As the clotting depends chiefly on the prothrombin, the thrombokinase, the fibrinogen and the calcium concentration, it is reasonable to suppose that also the retraction is influenced by these factors.

The rôle played by the calcium and the thrombokinase has already been mentioned. That of the fibrinogen was studied by means of a series of mixtures of hard centrifuged plasma and the corresponding serum, to which were added suitable quantities of citrate. In this manner a number of solutions were obtained, containing different amounts of fibrinogen, but otherwise of the same composition except as regards prothrombin and thrombin. That these two elements were not present in the same amount in all the solutions is probably of minor importance, though, inasmuch as the prothrombin in the process of clotting is converted into thrombin; and provided that there is the same amount of thrombin in the serum as of prothrombin in the plasma, — which is not the case, though, — the total amount of thrombin should then be the same in all the mixtures. To each of the latter there was then added the same quantity of an emulsion of platelets, whereupon the clot-retraction was tested. It was found that the retraction was greatest when the amount of fibrinogen — determined by Gram's (4) method — was smallest (Table V). The explanation of this is possibly the sponge-like structure of the precipitated fibrinogen, in the meshes of which

the serum is held. The larger these meshes are, the more difficult will it be for the sponge to hold back the serum, and the more easily will the retraction take place.

I have not been able to make serial experiments with varying amounts of prothrombin, but I have examined the retraction in a number of patients with reduced prothrombin contents in the plasma (determined by Lehmann's (7) method). I found that a low prothrombin content does not have any effect on the retraction unless the clotting is very slow, which is only the case with exceedingly low prothrombin values. If the clotting time is very long, however, the retraction, too, will begin late. This is the case, for instance, in hemophilia; but in such cases the clotting time may be shortened by the addition of tissue thrombokinase, which does not affect the retraction; and it will then be seen that the clotting begins very soon, whereupon the clot retracts with normal speed.

As might be expected, the retraction of the clot is very much dependent upon the temperature. As may be seen from Table VI, it is rapid 37° C, very slow at temperatures around the freezing point. It is further seen that the retraction is almost the same at 37° and at 30° C, which means that slight variations in the temperature of the water bath within these limits do not materially affect the results.

Finally must be mentioned the results of studies on a series of normal individuals. On the average, a retraction of 2 cm³ was reached in 30 minutes; forty minutes must, however, be considered as the normal. The diagram Fig. 7 shows the distribution in a normal material.

The method described in these pages may of course be modified if it should at any time later be found of advantage, for instance

Table VI.
The effect of the temperature on the retraction.

Temperature	Time required for the expression of 2 cm ³ of serum (minutes)
37° C	26
30° »	28
21° »	70
3° »	1440

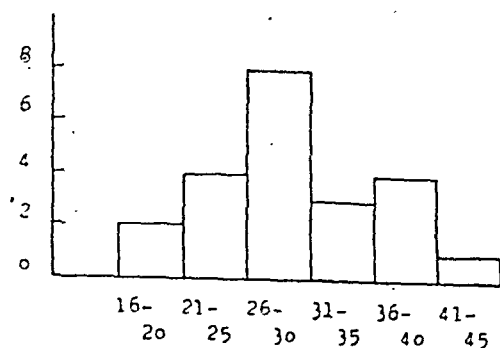


Fig. 7. — Diagram showing the distribution of the retraction time in a normal material. — *Abscissa*: the retraction time. *Ordinate*: number of persons.

in using blood or plasma the clotting of which is prevented by other means than those employed in the present experiments. It may also be used, of course, to study the dependence of the retraction on other factors such as, for instance, the salt concentration and the pH. An investigation of the latter, especially, might have been of interest; but as my experiments were carried out in a hospital laboratory I lacked the apparatus necessary for the purpose. Of my results from the clinic, with this method, a report will appear later elsewhere.

Summary.

After some brief remarks on the physiologic and clinical importance of the clot-retraction of the blood and mention of diverse methods for the study of this process, the author describes his own method of using citrated plasma, which is recalcified, instead of blood, — a method which, as he shows, offers several advantages. His experiments resulted in the following observations:

- 1) An excess of calcium chloride hinders the retraction.
- 2) The retraction depends chiefly on the number of blood platelets in the plasma, and not on the thrombokinese.
- 3) The retraction diminishes with increasing concentration of fibrinogen.
- 4) When the plasma is allowed to stand for a time at 37° C, its power to retract is reduced, whereas its coagulability increases.
- 5) Within certain limits the retraction is independent of the plasma's content of prothrombin.
- 6) The retraction takes place much more rapidly at a temperature about 37° C than at room- or lower temperatures.

7) Microscopic studies of the clots have shown that if retraction has taken place the fibrin threads lie disposed in a characteristic reticular formation, otherwise not.

My grateful acknowledgment is due to the Trustees of the Miss P. A. Brandt Fund for placing at my disposal the apparatus used for the experiments described in this paper.

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Mumps meningitis and meningo-encephalitis.

By

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(Submitted for publication August 7, 1942).

This paper will deal with the cases of mumps meningitis and some cases of mumps meningo-encephalitis that have been under treatment in the Frederiksberg Hospital in the period from October 1941 to May 1942 inclusive.

According to the literature, serous meningitis associated with mumps is a rather infrequent occurrence. The frequency is stated to vary in the various epidemics and countries from 0 to 10 per cent of the total number of patients attacked by mumps (1, 5, 8, 13, 17, 19). In Stockholm this constellation was observed only in 10 cases during the period of 1924—34, and then in 70 cases in 1936—40, with no less than 24 cases in 1940 (2). The Danish Public Health Statistics give no information about this form of meningitis, and only a few cases have been reported in this country (11, 12, 15, 18). It seemed reasonable to assume, however, that the lesion is somewhat more frequent than given in the literature, as it may take such a mild course that meningitis cannot be diagnosed with certainty unless the spinal fluid is examined (7). Further, cases have been reported that show indisputably that serous meningitis may be the first and only clinical manifestation of an infection with the virus of epidemic parotitis (2, 3, 4, 16, 20, 22). The etiology of

the serous meningitis may readily remain obscure if attention is not paid to the possibility of infection with the virus of mumps.

As is well known, the virus which brings about the appearance of mumps attacks preferably the salivary glands, pancreas and gonads, less frequently the meninges, brain and peripheral nerves. In a greater majority of cases the course of the infection is characterized by the swelling of the parotid gland, which has given the disease its name. When other organs are attacked it usually happens after the parotitis has persisted for some length of time. Thus the meningitic symptoms are said to appear within 14 days after the onset of mumps, occasionally even later. The symptoms are the usual pressure phenomena, headache, dizziness, nausea and vomiting, accompanied by elevation of the temperature to 38—40° C. There is rigidity of the neck, and many authors state that Kernig's sign is present. Lumbar puncture shows either a normal or increased pressure, and the spinal fluid shows a more or less pronounced pleocytosis, the highest number of cells recorded being 2500 per cm^3 (6). The cells are mostly mononuclears, but, as in other forms of lymphocytic meningitis, polynucleosis may be present early in the disease (8, 9, 22). The protein reactions are normal and the glucose concentration is normal or slightly increased. Cultures from the spinal fluid show no growth.

As a rule, the disease takes a mild course, only very rarely terminating fatally. It is the consensus of opinion that there is only slight agreement, or none at all, between the intensity of the clinical symptoms and the pleocytosis of the spinal fluid. The temperature usually subsides to normal level in 4—6 days, and the patient is rapidly free from symptoms. Thus the prognosis *quoad vitam* is good in the acute stage of the disease, but how the patients get along subsequently is still an open question, as no follow-up investigation has been reported that shows whether mumps meningitis may later turn into a chronic meningitis.

The diagnosis is easy in the presence of parotid swelling or orchitis, but otherwise it has to be made by exclusion and through a careful anamnesis, which may give a good deal of differential diagnostic difficulties, as besides mumps meningitis one has to consider other forms of lymphocytic meningitis, *e. g.*, aporalytic polymyelitis, tuberculous meningitis, zoster meningitis without zoster, abortive encephalitis taking a course like that of serous meningitis without

symptoms of encephalitis, the serous meningitis of Weil's disease, and septic meningitis as a phenomenon of intoxication in septic conditions.

If the brain is involved the cases are usually more severe, more frequently associated with dizziness, drowsiness, pareses and reflex and sensory disturbances. Often the border-line between mumps meningitis and mumps encephalitis cannot be drawn, and hence the designation *mumps meningo-encephalitis* is employed by many authors. The pleocytosis of the spinal fluid behaves quantitatively and qualitatively as in the meningitis, but perhaps it is not quite so pronounced in the more encephalitic cases. The protein reactions show slightly increased values. The encephalitic affection is more protracted, and its prognosis is less favorable; for instance, permanent defects may remain in the form of acoustic or optic atrophy (4, 10, 13, 21).

Myelitis is a very rare sequela of mumps. *Peripheral neuritis*, in various forms, is seen somewhat more frequently, though presumably due to a meningo-radiculitis resulting from the meningitis. *Mental disturbances* may occur, most often in connection with orchitis, in the form of acute (febrile) delirium, hallucinations and, though rarely, manic or depressive conditions (14).

In Dep. E of the Frederiksberg Hospital, which receives patients from the municipality of Frederiksberg and from Copenhagen County, with a total population of about 333,000, no instance of mumps meningitis was seen from the erection of this department in 1939 to the outbreak of the mumps epidemic in the winter of 1941—42. According to the report from the City Board of Health, from 28/9/41 to 30/5/1942 there occurred altogether 7820 cases of acute epidemic parotitis in the district of this department. Within this period 106 cases of mumps meningitis were admitted to Dep. E, i. e., 1.34 % of the total registered number of cases of mumps. Table 1 gives the age and sex distribution of these 106 meningitis patients.

From Table 1 it is seen that of the 106 patients 62 (58 %) were under 16 years, and of the total number of patients the males are decidedly in the majority, making two-thirds of the total. In this connection it may be mentioned that in the abovementioned material of 70 patients with mumps meningitis from the St. Erik's Hospital, Stockholm, Ahlberg (2) found 70 % of the patients to be over 15 years.

Table 1.

Age and Sex Distribution of 106 Patients with Mumps Meningitis.

Age	Male	Female	Total
0—5	13	6	19
6—10	24	7	31
11—15	7	5	12
16—20	13	5	18
21—25	3	4	7
26—30	6	3	9
31—35	0	3	3
36—40	2	2	4
41—45	2	0	2
46—50	0	1	1
Total	70 (66 %)	36 (34 %)	106

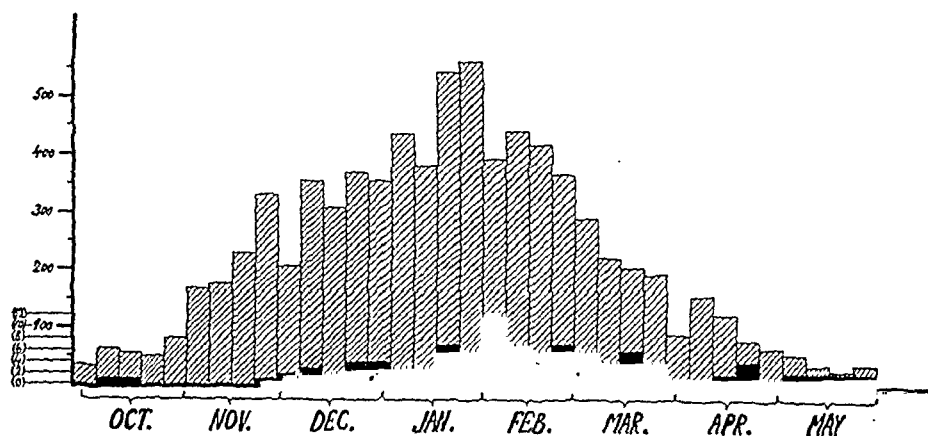


Fig. 1. Chronological distribution of epidemic parotitis and mumps meningitis in the mumps epidemic of 1941—42.

▨▨▨▨: Cases of epidemic parotitis (notified cases per week in the district).
 ■: Mumps meningitis (number of admitted cases per week $\times 10$) — numbers given in brackets along the ordinate.

Fig. 1 gives a graphic presentation of the chronological occurrence and the numerical proportion between the incidence of epidemic parotitis and that of mumps meningitis. For the sake of space, in the plotting of the numbers of cases, the incidence of meningitis is magnified 10 times in relation to that of parotitis.

Fig. 1 shows that the number of admitted meningitic patients increases in fair agreement with the increasing parotitis epidemic, the incidence of the two lesions culminating practically at the same

time. On the other hand, the incidence of meningitis decreases more slowly than does the epidemic, suggesting that in the course of the epidemic the virus has a gradually increasing tendency to attack the meninges. The indications for the performing of lumbar puncture were not changed during the period in question.

Of the 106 patients with serous meningitis, 77 had positively been exposed to infection with mumps. The anamnesis was practically the same for all the patients: As a rule, an abrupt rise in temperature to 39—40°, accompanied by headache (most often frontal) with nausea and vomiting, in some cases with dizziness, too, followed soon after by pain in the back and neck, often with difficulty in sitting up in bed. In the younger children, as seen so often, the symptoms commenced with pain in the abdomen, and this symptom occurred in a few adult patients, too (pancreatitis). The general condition of the patients was good; and they were not confused, anxious, screaming, smacking their lips, grimacing or gnashing their teeth. A few patients presented a rapidly subsiding vasolability with complete or partial redness of the face or neck, together with dermographism. No disturbances of the cranial nerves were observed, apart from a slight mydriasis in a few cases. No pareses or reflex disturbances could be demonstrated. Examination of the sensibility could not be carried through consistently. The most important clinical symptom, however, has been the *rigidity of the neck and back*, which was present in every case.

The disease took invariably a mild course. Here in the hospital the patients have all been clear and orientated, with no sign of anxiety or mental disturbances. The chief complaints have been headache, nausea and, occasionally, dizziness, besides some pain in the neck and back on movements.

In the great majority of these cases the meningitic symptoms commenced 2—8 days after the appearance, of the parotid swelling — in 3 patients, however, not until respectively 15, 15 and 20 days after. The last-mentioned 3 patients had parotid swelling for 3—8 days, and then they were symptom-free till the meningitic symptoms commenced. In 3 other patients the meningitis commenced on the same day as the swelling of the parotid. Finally, 3 patients had meningeal complaints respectively, 2, 2 and 9 days *before* the swelling of the parotid; only in one of these cases did we have an opportunity to perform lumbar puncture — on the day before the appear-

ance of the swelling of the parotid — in order to establish the diagnosis of serous meningitis.

In 5 of the patients with serous meningitis *no affection of the parotid or other salivary gland could be ascertained, neither clinically nor anamnestically*. All five patients have positively been exposed to affection with mumps and the meningitis made its appearance within the incubation period. Two additional patients without parotid swelling had probably, but not quite certainly, been exposed to an infection.

The temperature fell off by lysis in 2—12 days. The headache has lasted 1—12 days; in many cases its duration was abrogated after lumbar puncture, and when the headache returned, a repetition of the lumbar puncture gave almost instantaneous relief — especially in patients in whom the spinal fluid pressure was increased. On the other hand, the lumbar puncture had no effect on the duration of the fever. The rigidity of the neck usually subsided within a few days, whereas rigidity of the back lasted longer, subsiding most often in 7—18 days. With the exception of 7, all the patients were discharged as well about 3 weeks after admission. None of the patients died.

All the meningitic patients but one were submitted to lumbar puncture immediately after their admission. Of these 105 patients 73 were repunctured 8 days later, and 36 of the latter were punctured again a week later. The cell count of the spinal fluid was invariably ascertained within 1—2 hours after the puncture. At the same time some of the fluid was set aside for glucose determination, which was invariably carried out after the Hagedorn-Norman Jensen method, NaOH and ZnSO_4 being added at once, followed by boiling, and then the analysis was continued later on. Examination of the spinal fluid showed the following features:

Pressure (Claude manometer): A good many of the measurements are uncertain or worthless, on account of the restlessness and tightening presented by many of the patients — often by the children. In about 75 % of the patients, however, the pressure was found to be 200 mm water-pressure or more, and in a few patients who kept perfectly quiet it reached up to 500 mm water-pressure.

Cell count (Fuchs-Rosenthal's counting chamber): All the 105 punctured patients showed pleocytosis, but no relation could be

demonstrated between the degree of the pleocytosis and the intensity of the clinical symptoms.

The cell count in the spinal fluid on admission of the patients is recorded in Table 2. (Lumbar puncture was not performed in 1 case.)

Table 2.

Cell Count in the Spinal Fluid; Puncture performed immediately after Admission.

Cell count per mm ³	No. of cases				
0— 25/3	7	15.2 %	77.1 %	
26— 50/3	3			
51— 100/3	6			
101— 200/3	14	52.4 %		
201— 300/3	9			
301— 400/3	10			
401— 500/3	6			
501— 750/3	16			
751—1000/3	10			
1001—1500/3	7				
1501—2000/3	8				
2001—3000/3	5				
3001—4000/3	3				
4001—5000/3	0				
5001—6000/3	1				
Total	105				

From Table 2 it will be noticed that about three-fourths of the patients showed a cell count under 1000/3; about one-half of the patients showed less than 500/3, and 15.2 % (16 cases) showed under 100/3. The highest cell count observed was 5203/3. The normal limit is reckoned to be 10/3 cells.

A differential count of the cells showed a great preponderance of mononuclears. In a few cases, however, a few percent of polynuclear cells were seen, most often early in the disease.

It is to be mentioned that of the total 110 cases of mumps *without* meningeal symptoms under treatment at the same time in Dep. E, lumbar puncture was performed on 17 without showing any pleocytosis in the spinal fluid (*i. e.* the cell count did not exceed 10/3). Further, in 5 mumps patients with meningeal phenomena and rigidity of the neck, the spinal fluid pressure was increased in 2 cases but the spinal fluid was otherwise normal.

In the cases where lumbar puncture was repeated an attempt has been made to follow the decrease in the pleocytosis as shown in Fig. 2.

From Fig. 2 it will be noticed that the decrease in the cell count at first was abrupt, later more slow, and present in a moderate degree even after 3 weeks of illness.

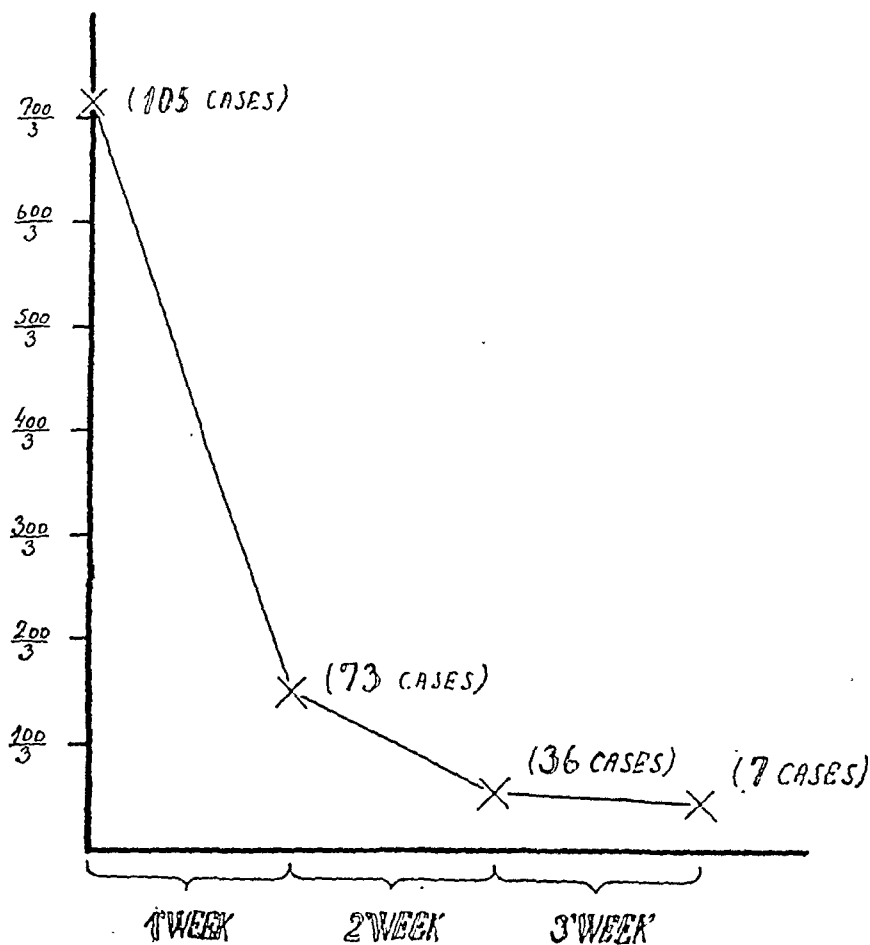


Fig. 2. Decrease in pleocytosis of the spinal fluid as ascertained on repetition of lumbar puncture.

The *albumin and globulin values* were normal or slightly increased: in 18 cases the albumin value was greater than 10 (20 in 16 cases, 30 in 2); in 23 cases the globulin value was found to be 2, in the rest of the cases, 1.

The *spinal fluid sugar concentration* was normal (45—60 mg %) in 65 % of the cases, between 60 and 80 mg % in 30 % of the cases, and above 80 mg % in more than 5 % of the cases.

Cultures from 64 specimens of spinal fluid on blood agar and ascitis fluid agar showed no growth; no cultures were made from the remaining 42 specimens.

Examination for *urinary diastase* (Wohlgemuth-Fabricius Møller's method) on the day after admission in 83 cases gave a normal value (< 200) in 23 % of the cases, a doubtful increase (200—300) in 25 %, whereas in the remaining 52 % of the cases the value was positively increased (300—600); in 3 cases it was even 1200.

Of the 70 male patients 10 had also orchitis; of the 36 female patients, only 1 had oophoritis — that is, the gonads were affected in altogether 10.4 % of the cases.

The *prognosis* appears to be good. From 50 answers to about 70 enquiries it is evident that 47 of these patients were feeling perfectly well 1—6 months after their discharge from the hospital and after the recommended recreation, usually of short duration. On re-examination 1 month after discharge, 1 patient presented signs of marked neurasthenia, but undoubtedly this represented an aggravation of a constitutional affection; 2 and 3 $\frac{1}{2}$ months after their discharge, two other patients complained of tiredness, headache, palpitation of the heart, anxiety and emotional instability, probably because their poor social conditions had precluded any recreation. At the reexamination, none of these 3 patients showed any sign of encephalitis.

Besides the above-mentioned cases of mumps meningitis, in the same period 5 patients were admitted with mumps meningo-encephalitis: 4 male respectively 7, 8, 17 and 43 years old, and 1 female of 26 years.

Of these 5 patients, 4 had swelling of the parotid when the entered the hospital. In these patients the clinical picture was more serious than in the preceding group of meningitic patients. All 5 patients had distinct meningeal symptoms, and at the same time they were hazy and drowsy, one with smacking of the lips, grimacing and complete loss of consciousness, and one was markedly psychotic on admission with motor restlessness, haziness, twaddle, and marked retrograde amnesia. In these patients the illness took a more protracted course, except for the highly acute phase due to the meningitis; the headache was more persistent, the temperature subsided more slowly. One patient was subfebrile for about 2 months after an interval of two weeks immediately after the menin-

gitis, when the temperature was normal and the patient was feeling well. In the more chronic (encephalitic) phase, slight isolated paresis (central facial paresis) developed in 2 cases; one patient had transitory dimness of vision and diplopia; one patient had a temporary impairment of the hearing. The chief complaint common to all of them was a very pronounced tiredness.

The spinal fluid was examined every week, with the following findings:

The *pressure* was slightly increased, as in meningitis.

The *pleocytosis* showed no relation whatever to the clinical picture of the cases. In the case of one patient (aged 43, with psychosis) there was occasion to examine the spinal fluid through a considerable length of time, and here the cell count was increased (26/3) as long as 12 weeks after the onset of illness. The *albumin reactions* were moderately increased.

The *spinal fluid sugar concentration* was normal.

Cultures showed no growth.

As to the *prognosis* nothing definite can be said on the basis of such a small material and with such a short observation period (4—5 months). One patient (17 years old) died of an intercurrent sepsis 8 days after admission. In the remaining cases one or more symptoms of the encephalitis persisted, even though there was some improvement. The psychotic patient was still under treatment in the Psychiatric Department 6 months after the onset of illness; he has continuously been hazy, sometimes restless, with impairment of memory and impressionability; he is aware of his condition and greatly impressed on this account. The neurologist and psychiatrist think his psychosis is due to the mumps encephalitis.

Discussion.

It has been mentioned already that the designation meningo-encephalitis by many authors is applied to all cases in which the central nervous system is attacked by the virus of mumps. The basis for this has been the experience that mumps encephalitis is always accompanied by a serous meningitis. Neither clinically nor pathologic-anatomically, however, is there any definite evidence to the effect that mumps meningitis always is accompanied by encephalitis. To us it seemed preferable, therefore, to employ the term

mumps meningitis in the cases presenting clinical signs of meningitis alone, while the designation mumps meningo encephalitis is applied to patients who, besides meningitis, show clinical signs of encephalitis, too.

In the present epidemic not only the morbidity has been extraordinarily high, but also the number of patients with involvement of the central nervous system appears to have been strikingly great. Further, there is also a great deal of evidence to the effect that, in particular, orchitis and also pancreatitis have been more frequent than usual, but this cannot be decided with certainty as mumps ordinarily is not reckoned as a cause for hospitalization; only in the presence of the more alarming symptoms of meningitis and orchitis are the patients admitted with mumps. As to the cause of the character of the present epidemic, nothing can be said except that it must be due to a strain of virus with neurotropic as well as gonadotropic and pancreatropic properties. The neurotropic property is evident from the fact that in 8 months no less than 106 patients were admitted to Dep. E for mumps meningitis — *i. e.*, 1.34 % of the 7820 cases of acute epidemic parotitis notified from the district of this department. This figure cannot be taken as an expression of the actual frequency of meningitis, however, as in mild cases the meningitis diagnosis may be difficult to make without lumbar puncture. In some of our patients with headache and an insignificant rigidity of the back, lumbar puncture has revealed a definite pleocytosis in the spinal fluid. Several cases of this kind may remain undiagnosed in practice, and most likely no physician is summoned in such cases, so that they are not included in any notification. It is reasonable to assume, moreover, that several cases of meningitis have been diagnosed at the home of the patients, but they are notified as cases of mumps, as mumps meningitis is not specified among the lesions which the physicians have to notify the City Board of Health. So our material is not comparable with the statistics from other places where the meningitis morbidity has been up to 10 %, as these figures originate from schools or army barracks, where every person attacked is hospitalized and examined with a special view to the presence of meningitis.

Over 50 % of our 111 patients with meningitis and encephalitis showed an unquestionable increase in the value for urinary diastase, and about 10 % had orchitis (1 had oophoritis). Among the 110

mumps patients admitted without affection of the central nervous system the corresponding figures were about the same. From the total mumps material it appears as if, next to the parotid gland, the pancreas was the organ most frequently attacked, then the gonads, then the meninges, and, least frequently, the brain.

It is rather surprising how little these meningitis patients were affected in spite of the greatly increased cell count in the spinal fluid. They were all perfectly clear, and only a few of them have been drowsing a little, but none of them presented any signs of the hyperesthesia or motor restlessness that are so characteristic of purulent and tuberculous meningitis. The most reliable symptom of meningitis, rigidity of the back, was present in all the patients. This symptom is always more pronounced than rigidity of the neck, and not infrequently has a patient presented a distinct rigidity of the back and no rigidity of the neck. This might be taken to indicate that mumps meningitis is predominantly a spinal meninitis, as rigidity of the neck is most conspicuous in basal meningitis. It is to be mentioned, too, that Kernig's sign has been demonstrable but rarely, notwithstanding a rather pronounced rigidity of the back and neck.

In contrast to the meningitis, the meningo-encephalitis is a serious disease, although we shall not venture to say anything about the prognosis with such a small patient material and such a short observation period as in our cases. As far as may be judged from a review of the available literature, the instance of psychosis here described is rather unique in character. Rather protracted psychosis has been observed in a few other cases as manic or depressive states, whereas delirium and haziness have been of fairly brief duration. Our patient is able himself to perceive and judge of his own phenomena of haziness, restlessness and dementia-like symptoms.

On autopsy of the one encephalitis patient who died of an intercurrent sepsis of unknown origin, the findings were stamped by the bacterial infection to such an extent as to preclude any definite conclusions from the autopsy findings; in keeping with the diagnosis encephalitis, however, there was oedema of the brain. Further, microscopic changes were demonstrated in the parotid, corresponding to the changes usually found in mumps although this patient had not had any clinically demonstrable swelling of the parotid. As

our material includes 5 unquestionable and 2 less certain cases of mumps meningitis without swelling of the parotid, the question as to whether an affection of the parotid has been present, but merely not clinically demonstrable, has to be taken under consideration. Still, in 3 of the patients the meningitis was demonstrably present respectively 2, 3 and 9 days before the swelling of the parotid appeared; and in one of these cases, moreover, the diagnosis of meningitis was verified by lumbar puncture on the day prior to the appearance of the parotid swelling, while in the two other cases the diagnosis was made clinically by the family physicians who sent the patients to the hospital. Such cases of mumps meningitis before or without any clinically demonstrable swelling of the parotid has been described only in a few cases in the literature, where the meningitis usually is reckoned as a «complication» of the mumps. From a clinical point of view, in our opinion, it seems more reasonable to look upon the mumps meningitis as a concurrent, sometimes primary, manifestation of the same virus infection.

Summary.

The material comprises 106 patients with mumps meningitis and 5 patients with mumps meningo-encephalitis.

In a greater majority of these cases the meningitic symptoms commenced 2—8 days after the appearance of the parotid swelling, in 3 patients respectively 15, 15 and 24 days after. Meningeal complaints prior to the swelling of the parotids were recorded in 3 cases, in one of which the diagnosis meningitis was verified by lumbar puncture on the day before the swelling of the parotids. In 5 patients it was impossible, clinically as well as anamnestically, to demonstrate any lesion of the parotid or other salivary gland, but all 5 patients had positively been exposed to the infection.

The most reliable symptoms of a serous meningitis are rigidity of the back and pleocytosis in the spinal fluid (monocytosis). The highest cell count in the spinal fluid was 5203/3 per mm³. The course of the disease has been mild and most of the patients were discharged from the hospital as recovered, 3 weeks after admission.

On reexamination of 47 patients, all were found to be well (observation period 1—6 months).

The meningo-encephalitis is a far more serious affection which may give permanent impairment in the form of isolated pareses or psychosis (observation period up to 5 months).

The authors do not look upon mumps meningitis or meningo-encephalitis as complications of acute epidemic parotitis, but take them to be concurrent, often primary, manifestations of the same virus infection.

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Neurosis cordis.¹

By

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Cardiac neurosis (neurosis cordis) is generally taken to signify a condition encountered in nervous asthenic persons that is characterized by a labile heart action. As a rule, these patients present no abnormality on examination of the heart, nor on roentgenography or electrocardiography. It is looked upon as an unimportant symptom complex in some neurasthenics. There appears to be a gradual transition, however, from this simple cardiac neurosis to more massive cardiac paroxysms which may perhaps be designated as neurosis cordis organica.

Under the term organic cardiac neurosis I include all cases presenting transitory changes in the neuromuscular system of the heart — changes that may be more or less demonstrable. The most characteristic cases are the ones that show distinct electrocardiographic changes during an attack, whereas the electrocardiogram is perfectly normal outside the attacks. Paroxysmal tachycardia may be set up as prototype of this affection. Other examples are found in transitory extrasystolia, auricular fibrillation and auricular flutter. It looks, however, as if many different electrocardiographic changes, may be represented in this group of lesions — changes which ordinarily are taken to be very massive and yet they

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may surprise the clinician by disappearing spontaneously in particularly favorable cases. Previously, in *Ugeskrift for Læger*, 1938, I have reported an instance of transitory heart block, of which we are unable to find any other explanation than that it was of neurogenic-reflex nature. This case is not unique, some cases of the same kind having been described in the literature, though not many; for it still seems to be an infrequent phenomenon that such a severe morbid change appears as an entirely paroxysmal feature.

It is characteristic of the group of lesions I shall mention that the cardiac paroxysms involved are seen most often in young persons whose heart in the clear-cut cases is not ailing at all; but, of course, it is also seen as a complication of more serious heart lesions. When this group of affections has attracted my interest, it is partly because it is more frequent and more important than generally assumed, and partly because it implies the pleasant possibility that the patient may recover completely — something we otherwise are not used to see very often in dealing with heart lesions.

I shall briefly review the case histories of some patients who have been admitted to the Medical Department of the Svendborg County and City Hospital, and in doing this I shall disregard the quite ordinary and well-known cardiac paroxysms.

Case 1.

This patient is an unmarried woman of 50 years who had been very nervous for the last couple of years, with indefinite cardiac complaints for which she had been treated with many kinds of remedies. In the last six months the symptoms have become more characteristic, with functional dyspnea and tendency to oedema of the legs in the evening.

Ordinary physical examination presented no definite abnormality, but the electrocardiograms showed the typical picture of bundle branch block with preponderance of the left side. She was treated with rest in bed and theobromin. When she had stayed in the hospital 10 days, the diuresis suddenly increased from about 600 cm³ to almost 2000, at which level it kept for some days and then fell off again to a normal level. The examination was repeated but revealed no abnormality. On the other hand, a new electrocardiogram showed that the bundle branch block had disappeared. There was still preponderance of the left side, but no definite signs of degeneration. This state remained unchanged.

From the day when the diuresis commenced to rise, the patient looked considerably more healthy than before. When later she was permitted to get up, she had no longer any heart symptoms, the functional dyspnea had subsided, and there was no tendency to oedema of the legs. She was feeling

perfectly well when she was discharged from the hospital, with instruction about returning if the symptoms turned up again.

So the diagnosis was: Transitory bundle branch block of unknown origin.

Unfortunately, she was indignant about the treatment given her in our department. Half a year later she was admitted to the Department of Surgery, and now she again had bundle branch block, which remained constant.

Case 2.

This patient was an unmarried cowman, 34 years old, with a past history of good health. Eight months before admission he had commenced to be troubled a little by functional dyspnea; in addition, he had almost daily some attacks of cardiac discomfort that would come apparently without any cause. One of these attacks had been so severe that he fainted, on which account he had been admitted to the Middelfart Hospital for some weeks. He had kept to his bed some days before his admission to our department.

On admission he appeared to be greatly exhausted, dyspneic and cyanotic, with threatening oedema of the lungs and pronounced congestion of the liver. The heart was greatly dilated, with ictus in the axilla. The heart action was 120, regular. An energetic stimulating therapy was instituted, under which he improved surprisingly rapidly. Four days after the institution of treatment, there were no longer any demonstrable phenomena of stasis, and roentgenography showed the heart to be normal in form and size.

Electrocardiography during the attack showed regular tachycardia, 120 beats per minute, strikingly small, initial complexes, left-sided preponderance and iso-electric T waves. Subsequent electrocardiograms showed a left-sided preponderance, but otherwise fair initial complexes, iso-electric T_1 and negative T_2 and T_3 ; now and then, a ventricular extrasystole.

On enquiry at the Middelfart Hospital it was found that the attack he had had 4 months before was precisely like the one described here. This goes strongly against the possibility of myocarditis or coronary thrombosis; and the sedimentation rate was only 3 mm. With the lesions mentioned, indeed, such a rapid and complete restitution was not to be expected.

The diagnosis was therefore: Cardiac paroxysm of unknown nature and origin. He had no cardiac symptoms whatever at his discharge from the hospital, and recently, that is, about half a year after his discharge, he was seen to make one of the steepest hills of the town on his bicycle.

Case 3.

This patient is a woman, aged 33, married to a painter.

One year ago she had an attack of rheumatic fever for which she was treated at home through two months. Since then, she has been troubled with palpitation of the heart and functional dyspnea. She has recently gone through pregnancy without any real aggravation of the symptoms.

The parturition took place in a hospital. On account of her heart lesion, cesarean section was performed in the 8th month, and tubal sterilization was performed at the same time. There were no cardiac phenomena in connection with the parturition, but two weeks later she began to have an uncharacteristic attack of oppression in the chest, dyspnea and anxiety, on which account she was transferred to the Medical Dep. of the Svendborg Hospital.

On admission to this department she was found to be a little dyspneic and cyanotic. The heart action varied between 100 and 140, with several extrasystoles periodically, but otherwise no particular abnormality. No signs of stasis. After she had been here three days she had a typical attack of paroxysmal tachycardia, but it subsided again before it could be registered. Electrocardiography showed regular tachycardia, with about 100 beats per minute, negative T_2 and T_3 and a few ventricular extrasystoles. As she was continually troubled by her attacks she was tentatively given chinidin (0.10×3). After this, her complaint subsided completely, and she could be discharged two weeks later. At that time there was no sign of any heart lesion. The electrocardiogram was perfectly normal except for a negative T_3 ; and roentgenography showed the heart to be normal in form and size.

The diagnosis was, therefore: Cardiac paroxysm of unknown origin. After the disappearance of these paroxysms her heart has to be regarded as normal.

Her case illustrates the importance of being acquainted with this group of lesions. She might perhaps have avoided the cesarean section and sterilization.

Case 4.

This patient is a woman of 61 years who for 3 years had been suffering from a mild degree of diabetes, for which she was treated with a very modest dose of insulin. 5 days before admission she was taken ill with diarrhea, and her condition was rapidly getting worse.

On admission the patient was comatous, giving off a strong odor of acetone. The blood sugar concentration was 700. In addition, the heart action was irregular and quite tumultuous; besides, oedema of the lungs was threatening. Electrocardiography showed auricular fibrillation, with tumultuous ventricular action. She was treated with insulin and bicarbonate, whereafter the acidosis was abolished and her general condition improved, but the heart action remained unchanged.

The patient was then given chinidin in increasing doses. When a daily dosage of 60 cg was reached, the rhythm of the heart became regular and quiet. She was discharged two months later, feeling perfectly well and showing no sign of any heart lesion. Electrocardiography revealed no definite degenerative signs, but roentgenography showed a slight enlargement of the heart.

In this case, the diagnosis was: Auricular fibrillation produced by her coma. She had not had any cardiac symptoms before admission, nor

did she have any at her discharge. So there is no reason to think she had any real heart lesion.

About 1 ½ years later the patient was readmitted to this department on account of an indefinite tiredness. Now she presented signs of a rather extensive bilateral pulmonary tuberculosis, but roentgenography of the heart showed only a slight enlargement, just as before, and the electrocardiogram showed a complete rhythm. She had had no real heart symptoms in the interval since her last discharge.

These examples illustrate how extensive and significant this group of lesions really is, when its entire scope is taken into consideration. Besides the aforementioned case of heart block, which has been published before, we here meet with 4 interesting cases. No. 1 had a transitory bundle branch block. No. 2 had a violent cardiac paroxysm, without showing any definite abnormality in the electrocardiogram. No. 3 had a more protracted paroxysm during which the records showed numerous extrasystoles, and once, paroxysmal tachycardia of short duration. No. 4 had transitory auricular fibrillation brought about by diabetic coma.

The question now arises with what right these cases may be regarded as neurogenic. A different interpretation would perhaps classify them as instances of acute myocarditis. In my previous work on paroxysmal heart block, I pointed out in detail how I arrived at the diagnosis neurogenic heart block. The sedimentation rate of the patient was not increased, and the block subsided suddenly, without leaving any prolongation of the deduction time. On recovery from a myocarditic block, we generally see a gradual transition from a complete block, over partial block to delayed conduction, which often takes months to become normal. In the cases cited here there was nothing to indicate that the patient was still suffering from some infection. The temperature was not elevated; nor was the sedimentation rate increased. And another interpretation to the effect that the lesion here might involve a coronary thrombosis is not very likely. Two of the patients were all too young for that, and the two others presented decidedly no evidence to that effect.

It appears to be characteristic of this group that the electrocardiographic changes very often are even unusually pronounced (complete block, bundle branch block, auricular fibrillation, and so on) — changes that otherwise are seen only in very advanced impair-

ment of the myocardium. It seems rather natural, however, that the electrocardiographic changes become violent just on nervous stimulation. To what extent we may speak of cardiac neurosis in such cases is still an open question.

This may be elucidated by some considerations on one of the most frequent changes: auricular fibrillation. Sometimes this phenomenon is seen in mitral stenosis, in which cases it appears to be massive and refractory to every form of treatment. One then gets the impression that the atria have been dilated and are gradually undergoing degeneration. On the other hand, in cases where the auricular fibrillation yields readily to treatment with chinidin, one is inclined to think it has been a matter of nervous irritation. This view finds support, indeed, in the fact that the tractable cases very often involve a Basedow heart, *i. e.*, lesion of a character that is strongly suggestive of changes in the nervous system and thus in the innervation of the heart, too.

Another group of patients in whom, it seems to me, we have to think of the possibility of neurogenic heart lesions, is, strange to say, the patients with diphtherial myocarditis. In the excellent work of Siggaard Andersen (1934) on diphtherial myocarditis, published in this journal, he has reported some extensive studies carried out in the Blegdam Hospital, from which he arrived at the conclusion that the serious myocarditis, which most often terminates fatally, comes in the acute stage of the disease. He also described a less serious form of myocarditis, however, which, in contrast to the first-mentioned, does not appear until the 3'—6' week of illness. Undoubtedly the primary myocarditis is a true myocarditis with severe clinical symptoms and electrocardiographic changes, showing on autopsy a quite extensive damage to the myocardium: acute hemorrhagic myocarditis. In the late and milder »myocarditis» there is no occasion for postmortem examination. Strange to say, it makes its appearance at the point of time when the temperature is normal and most often without affecting the temperature in any particular degree — and this happens at the very same point of time when the pareses make their appearance. It seems, then, to be convenient interpretation that we are here dealing with some form of paresis that involves one or some of the nerves that regulate the activity of the heart. So this late myocarditis might then be interpreted as a neurosis.

It is to be added that the possibility also remains of a myocarditis and a coincident nerve affection, as the myocarditis conceivably might produce reflex disturbances in the innervation of the heart (something that naturally may result also in coronary thrombosis and other heart lesions).

Recently I have had occasion to observe such a case. The patient was a probationary nurse who had had an attack of scarlet fever without being very ill. On the 14th day of illness she had some queer sensations in the heart region and palpitation of the heart, and the electrocardiogram showed a partial block. A few days later the electrocardiographic findings were normal again, without any delay in conduction. The symptoms had then subsided completely. Not until 6 weeks later did she again have some slight cardiac symptoms and now the electrocardiogram again showed a slight delay in conduction. When the latter findings have to be taken as evidence of the remains of a myocarditis, while the course of the acute attack decidedly indicated a nervous irritation, it seems to me that the explanation will have to be the one I have suggested: that the myocarditis in its initial stage through reflexes had produced a neurogenic block.

In this way we find a gradual transition to the heart lesions in which the myocardium is damaged to an extent that in itself is sufficient to give electrocardiographic changes.

The series of affections here described thus consists in 4 groups with gradual transitions. Firstly, simple cardiac neurosis associated merely with indefinite cardiac sensations, perhaps chiefly of functional character. Next, organic cardiac neurosis associated with cardiac paroxysms that can be explained as attributable to agencies involving the innervation of the heart, while the myocardium is not impaired. Then the cases in which an acute affection of the myocardium by way of reflex action brings about disturbances in the innervation of the heart. And, finally, the cases in which the cardiac symptoms are due to a lesion of the myocardium itself.

As a curious fact it maybe mentioned that the electrocardiographic changes in Group II will often be far more severe than those seen before. From this we may draw the somewhat paradoxical conclusion that, under certain conditions, severe electrocardiographic changes give a better prognosis than slight changes.

As to the causes of organic cardiac neurosis, several seem conceivable. Heart block has been described as arising from pressure on the vagus exerted by an oesophageal diverticulum when this was filled. But generally we shall not be able to find such a solid explanation. I have suggested already that the changes encountered in the nervous system in exophthalmic goiter may produce auricular fibrillation, perhaps also other disturbances in the heart action. When such changes may be seen in exophthalmic goiter, it seems obvious that other endocrine lesions may have a similar effect. One of the patients described here was suffering from diabetes. In this case, however, it seems more natural to look for the cause in the changes in the nervous system that may conceivably be produced by the acidosis during the coma, but nothing definite can be said about this point. Undoubtedly hyperinsulinism may constitute an eliciting cause. Other changes in the composition of the blood might conceivably also interfere with the innervation of the heart — *e. g.*, alkalosis or changes in the calcium content of the blood, or other changes in the chemical composition of the plasma. But here we have entered into an entirely speculative field.

We have more solid ground under our feet when we think of various medicamental agencies as the cause of the cardiac neurosis and here, of course, we think in particular of the cardiac remedies. It is well known that an overdosage of digitalis may give heart block that disappears again when the employment of digitalis is discontinued. Digitalis may also produce auricular fibrillation, which has a lesser tendency to spontaneous remission. Further, we have to keep in mind the remedies which exert a direct action on the nervous system — in particular, atropin, adrenalin, acetyl-cholin, and gynergen. Undoubtedly thyroid preparations will also be disclosed as a frequent cause of the cardiac neurosis. Finally, tobacco extrasystoles are to be mentioned here too. But a thorough examination and a very careful questioning into the past and recent history of the patient will often be necessary if we are to have any chance of finding the extraneous cause.

It would not be safe yet to try to establish any treatment for this variegated group of affections. If the cause of the lesion be known, of course, an attempt has to be made to abolish it. If this has no favorable effect on the lesion (for instance, auricular fibrillation produced by digitalis) or if the cause is unknown, at the

present we have to confine ourselves to experimental tentative treatment. The remedies that seem likely to have some favorable effect are primarily the drugs acting on the innervation of the heart, namely: adrenalin (sympathetic tonus), atropin (sympatheticolysis), acetyl cholin (vagotonus), and ergotamin tartrate, better known as gynergen (a sort of vagolysis). Further, digitalis which, besides being vagotonic, acts on the conduction system in the heart. The same applies to chinidin, which has proved very effective in auricular fibrillation and in certain forms of paroxysmal tachycardia. As far as that goes, many cases have a tendency to spontaneous recovery, and a good effect may be obtained simply by employment of ordinary sedatives.

As to the prognosis, it may be said to be good — at any rate in comparison with the prognosis of myocardial degeneration and valvular defects. Of course, an entirely neurogenic heart block may conceivably prove fatal, and other phenomena giving rise to marked decompensation of the heart may prove refractory to treatment. But these cases, I think, will rarely be described as neurosis, as the neurogenic nature of the lesion can be proved completely only on the disappearance of the lesion. Still, conclusions by analogy from similar cases — preferably, of course, from previous attacks in the same patient — may sometimes furnish a proof of probability that will further be corroborated by the absence of pathologic-anatomical changes. In general it may be said, however, that these cases will rarely have serious consequences, especially when they are treated effectively at an early stage.

Summary.

The writer has attempted to set up a new special group of affections within the cardiology — a group which he suggests to designate as *Neurosis cordis* (in extended sense of the term) or perhaps as *Neurosis cordis organica*. It covers transitory cardiac affections in which the myocardium presumably is not injured, while the appearance of the disease is attributable to changes in the innervation of the heart, morbid phenomena of which some are wellknown (e. g., paroxysmal tachycardia), and also the cases of auricular fibrillation in which a normal rhythm is reestablished, spontaneously or through treatment. Through some examples the writer points out

the serious functional disturbances one may encounter in such cases.

In his discussion of the question the writer has tried to show that many cases of acute cardiac phenomena, which generally are listed as myocardial affections, more likely are to be looked upon as belonging to this group. The possible causes of these morbid conditions are discussed and it is pointed out that they have to be looked for in endocrine lesions, intake of certain medicaments, or changes in the chemical composition of the blood (electrolytic shifting) — the last-mentioned most often of unknown nature.

It is yet too early to try to establish the treatment, but the writer calls attention to the remedies acting on the innervation of the heart or on the neuromuscular system.

The prognosis may be characterized as relatively good.

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Chief: prof. K. A. Jensen.

Inulin Clearance and the Determination of Inulin in Blood and Urine.

By

KAJ RØJEL.¹

(Submitted for publication August 7, 1942).

It may now be considered an established fact that the chief processes in the formation of the urine consist of glomerular filtration and tubular reabsorption. As a consequence of hydrostatic pressure in the glomerulus capillaries there is a transmission of a deproteinized filtrate from the lumen of these capillaries into the capsular space; the filtrate contains the filtrable constituents in the same concentration as plasma. During the passage of the filtrate through the tubules, the greater part of the water is taken up together with the so-called threshold bodies, e.g. glucose and NaCl; other substances, for instance urea, become highly concentrated in the tubules owing to the absorption of the water, but to some extent they return through the epithelial cells of the tubules to the blood — whether on account of active reabsorption or of passive diffusion is not quite certain; it is assumed that still other solids such as sulphates and kreatinine are neither reabsorbed nor diffused back in the tubules. In recent years we have learned to know of certain bodies foreign to the organism, mostly excreted by secretion processes in the tubule cells, for example phenol-red and perabrodil (diodrast) and other iodic substances used in urography. It is known of at any rate one of the normal constituents of the urine, kreatinine, that in man it is partly excreted by tubular secretion.

¹ This investigation was made with the financial assistance of the P.A. Brandt foundation.

When making clinical and — particularly — physiological investigations into the renal function it is of importance to know how much glomerular filtrate is formed per minute; for if we know this and the concentration of a filtrable substance in plasma, it is possible to compute how much of the substance filters out into the glomerules per minute. If at the same time we determine how much of this substance is excreted in the urine per minute, we can calculate the quantity of the substance reabsorbed in the tubules or diffused back or perhaps secreted.

If we know that a given substance is excreted solely by filtration in the glomerules and neither secreted nor reabsorbed in the tubules, this can be used for determining the quantity of filtrate (F) formed per minute. If we determine the plasma concentration (P) of the substance, its concentration in the urine (U) and the minute diuresis (D), we can set out the following equations:

$$M_1 = F \cdot P \text{ and } M_2 = U \cdot D$$

where M_1 is the quantity of the substance filtered per minute and M_2 the quantity per minute excreted with the urine. But as according to the above $M_1 = M_2$, we get

$$F \cdot P = U \cdot D \text{ or } F = \frac{U \cdot D}{P}$$

By the plasma clearance (C) of a substance we understand the number of c.c. plasma which the kidneys can purify of the substance in the course of a minute. C is found by dividing the quantity excreted per minute by P.

$$C = \frac{U \cdot D}{P} = F$$

From this it appears that the plasma clearance of a substance excreted solely by glomerular filtration and neither secreted nor reabsorbed in the tubules is equal to the quantity of filtrate formed per minute.

Consequently, one of the most important objects of renal physiology is to find a substance that complies with the said conditions: that it is filtered in the glomerules and neither secreted nor reabsorbed in the tubules. In the course of time several substances have been credited with these properties, with more or less justification, such as kreatinine, sulphate, ferricyanide, cyanol and tiourea.

In 1930 Marshall (1) showed that the urine of aglomerular fishes never contained glucose even when there was a high glucose content in the blood and/or after ingesting florizine. On the other hand it was easy to make the urine of glomerular fishes contain glucose: by administration of glucose, by florizinizing, or simply by manipulation of the fish itself. The same was true of certain other sugars: xylose, raffinose, succrose, inulin, etc., they were readily excreted by glomerular, but not by aglomerular fishes. From this the hypothesis was set up that in other animals too these sugars were excreted by glomerular filtration, but not by tubular secretion. As these sugars cannot be converted in the intermediate metabolism and therefore are of no value to the organism, it was thought — on the basis of teleological considerations — that reabsorption in the tubules might be ruled out.

In 1934 Richards, Westfall and Bott (2) suggested the use of the sugar inulin for clearance tests, and since then the importance of this substance as a means of measuring filtration has been established by a large number of publications from America.

Inulin is a polysaccharide occurring as a reserve nutriment in plants (3). Acid hydrolysis breaks it down into 93 per cent. fructose, 6 per cent. fructoseanhydride and 1 per cent. aldose. Acid-hydrolyzed inulin when reduction-titrated has a fructose equivalent of 94 per cent (93 per cent. fructose and 1 per cent. aldose), but when analyzed colorimetrically after being treated with diphenylamin it has a fructose equivalent of 99 per cent. (93 per cent. fructose and 6 per cent. fructoseanhydride) (4). The molecular weight lies in the vicinity of 5000 (cit. 4.5). Inulin is sparingly soluble in cold water but dissolves readily in hot water at 80° with up to 20 weight %; after cooling to 40° it forms a supersaturated solution which, however, is stable for several hours and thus permits of continuous infusion (6).

Inulin has the following properties, the presence of which must, according to Shannon and Smith (7), a priori be required of a substance to be employed as a measure of filtration:

- 1) It is determinable with sufficient accuracy in blood and urine.
- 2) It is non-toxic on all the experimental animals tested. In man there is sometimes a rise in temperature in conjunction with intravenous injection; this is presumed to be the result

of impurities; the pyrogenous effect can, it is stated, be removed by filtration through a Seitz filter (8).

- 3) It has no effect on the renal function, measured by the excretion of other substances (6, 9).
- 4) It is not consumed or converted and is excreted quantitatively in the urine (3, 6).
- 5) It is filtered and dialysed through collodium and similar membranes which, like the glomerulus membrane, is permeable to crystalloids but impermeable to colloids (2, 3, 6, 10).
- 6) It does not combine with the plasma proteins (2, 6).

To these may be added:

- 7) It is found in the plasma fraction of the blood and does not permeate the erythrocytes (11, 12). If the blood clearance is to be calculated from the plasma clearance of inulin, one must know the volume percentage of the erythrocytes.

It was to be expected from its ability to pass through collodium membranes that the inulin in the glomerular filtrate occurs in the same concentration as in the water phase of plasma; all the same as far as the frog is concerned it has been proved (10) by direct analysis of the filtrate in the capsular space obtained by capsule puncture.

It can scarcely be held that the absolute proof has been produced that inulin is excreted by filtration alone and that it is neither secreted nor reabsorbed; but we have substantial evidence to that effect.

Inulin is not excreted by aglomerular fish kidneys (3), but it is excreted in the urine after administration to fishes whose kidneys have glomerules.

Inulin is not excreted by the frog kidney when the substance is perfused through vena portae renalis, which supplies the tubules, but it is excreted when it is conveyed to the glomerules through arteria renalis (13). As regards dogs and rabbits, inulin is not excreted in the urine when the blood pressure is reduced below a certain level, whereby glomerular filtration ceases; that the function of the tubules under these circumstances is intact, at any rate partially, is shown by the continued ability of the kidneys to excrete phenol-red and diodrast, about which substances we know that they are preponderantly excreted by tubular secretion (13).

In all glomerular animals tested the value of the inulin output per minute is actually proportional to the plasma concentration and within the latter's values, from some few mg % to over 1000 mg% (6.9). This means that the inulin clearance is independent of the plasma concentration. This is what may be expected of a substance that is excreted solely by filtration. Conversely, it has been found that, with increasing plasma concentration, the quantity of the urinary output of substances that are mainly secreted by the tubules by cell activity asymptotically approaches a maximum corresponding to the maximum function of the tubule cells; the clearances of such substances therefore fall with increasing plasma concentration.

With dogs the clearances of inulin and kreatinine (9, 14), and of inulin, kreatinine and ferrocyanide (11) are identical under all the conditions examined. In florizinized dogs the clearances of inulin and glucose (9) and of inulin, glucose and xylose (3) are identical. With rabbits (15) the clearances of inulin and kreatinine agree completely.

In the tests referred to, and in several others contained in the literature, showing the same clearances for two or more substances, the clearance determinations have been made *simultaneously*. From this it follows that the substances are concentrated in the same proportions from plasma to the final urine quite independently of their plasma concentration; that is to say, they give the same concentration index, the same $\frac{U}{P}$. This is explainable alone by

the assumption of glomerular filtration of a fluid containing these substances in the same proportions as the plasma water, and of concentration by the reabsorption of a part of the filtered water.

Were we to assume that in addition there was a reabsorption or a secretion in the tubules of a part of these substances, this would presuppose 1) that the same fractional part of the filtered quantity of a given substance was always reabsorbed or secreted, and 2) that this fraction was the same for all the substances with identical clearances. As these presuppositions are unacceptable as being improbable, we must also reject the idea of tubular reabsorption or secretion of the same substances.

It is obvious that the determination of the inulin clearance is of great theoretical and scientific interest; but it is another question

whether inulin clearance tests will be of any great value in the clinic. With normal people (16) and with dogs (17) the urea clearance is fairly constant at about 50 per cent of the inulin clearance when the diuresis is maintained over 1.5—2 cm³ per minute. Therefore it is possible that in cases of reduced renal function the inulin clearance will provide no other information than the urea clearance.

Human inulin clearance is best determined by means of continuous intravenous infusion of the substance, whereby a suitably high and constant plasma concentration is secured. To human beings Shannon and Smith (6) give 100 g inulin in a 20 per cent solution by intravenous infusion over a period of 30 minutes; this induces a plasma concentration of 300—400 mg%, which falls to 100 mg% in from 90 minutes to 3 hours. The values of human inulin clearance are stated to be from 110 to 150 (18).

Inulin can be determined by acid hydrolysis and reduction titration by Shaffer and Somogyi's method (19) or colorimetrically — likewise after acid hydrolysis — by means of Ihl and Pechmann's reaction for fructose (20), which results in the substance acquiring a vivid blue colour when heated with a solution of diphenylamin in muriated alcohol.

Own Investigations.

For some time I have been working on inulin clearance tests on rabbits at the University Institute of General Pathology. The work is not yet completed and therefore will not be referred to here. However, as I encountered some initial difficulty with the inulin determination, which I secure colorimetrically, and as I am aware that experiments in various places on human inulin clearance have met with similar difficulties, I propose to describe the modification I have made in the methods published in the literature (21, 22); this modification does not claim to be essentially new, and indeed it may not even be the best and ultimate form.

I have had two difficulties in particular; one was that the blue colouring matter formed by the reaction with diphenylamine is sparingly soluble in water and diluted alcohol, so that it flocculates 1) if owing to excessive inulin content its concentration becomes too high and or 2) if the muriated alcoholic diphenylamine solution is diluted too far with water by adding too much of the watery

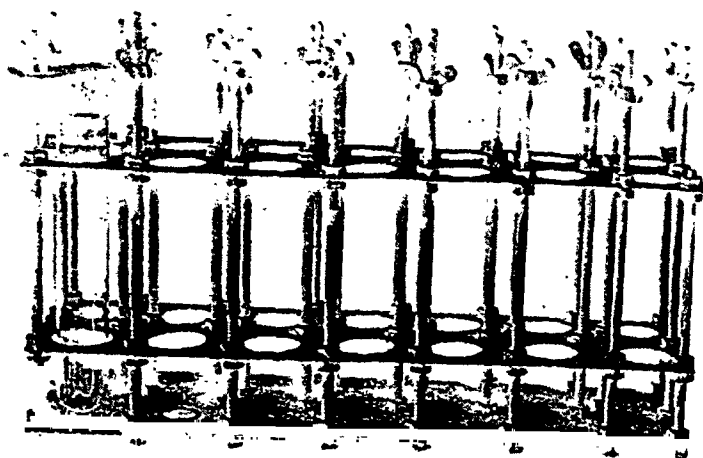


Fig. 1.

solution whose inulin concentration is being determined. On the other hand the inulin concentration must not be lowered below a certain minimum, as then the colour becomes too weak for exact colorimetric determination. For this reason, by means of a suitable dilution of serum and urine I aim at getting the inulin concentration to lie around 10 mg% and at any rate between 5 and 30 mg%. Of this dilution $\frac{1}{2}$ cm³ is added to 5 cm³ of the muriated alcoholic diphenylamine solution, whereby the water content of the mixture is only slightly increased.

The other difficulty consisted in heating the mixture in the water-bath, stoppered in order to avoid concentration through the evaporation of the alcohol. For this purpose I use test-tubes of Duran glass, 23 × 115 mm, which as a rule will tolerate the pressure and stand being cooled under the tap immediately after boiling. The tubes are closed with rubber stoppers, which are prevented from jumping up by placing the tubes in a rack (see fig. 1) and fastening a metal plate down over them.

I boil for half an hour in the water-bath, as I have found that after 15 minutes boiling the colour does not attain to quite the

same density as after 30 minutes, whereas no greater colour intensity is secured by boiling for an hour than after 30 minutes. It is important that the water is kept on the boil the whole time, and preferably in the stinkcupboard with the windows closed, as there is some risk of the tubes exploding. After boiling the tubes are cooled at once under the tap, and colorimetry proceeds immediately afterwards in a Duboscq colorimeter. If the tubes are allowed to stand for several hours there may be flocculation of the colour, even under these experimental conditions; when this has not happened I have observed no disturbing changes of colour after a period. It sometimes happens — for some uncertain reason, possibly because the tubes are insufficiently cleansed — that some tubes assume a distracting greenish tint; however, one is never in doubt when this happens, so that the analysis can be discarded to avoid any error.

Serum is analysed in the following manner:

The proteins are precipitated by Herbert's method (23): Pipette $\frac{1}{2}$ cm³ serum into a small centrifuge glass, add 1 cm³ distilled water, shake, add $\frac{1}{2}$ cm³ 10 per cent. ZnSO₄·7H₂O, shake, add $\frac{1}{2}$ cm³ 0.5 normal NaOH, shake, centrifuge. This gives a dilution of 1:5.

With a slight deviation the diphenylamine reagent is prepared according to Alving, Rubin and Miller (22): *a*, dissolve 10 g diphenylamine per analysis in 50 cm³ absolute alcohol; this stock solution is credited with keeping indefinitely in the dark; *b*, mix 70 cm³ absolute alcohol with 50 cm³ concentrated hydrochloric acid. The reagent is prepared by adding 5 cm³ of *a* to 80 cm³ of *b*; this will, it is stated, keep for a week; as a rule, however, I have made it fresh every time.

To $\frac{1}{2}$ cm³ of precipitated (and if required diluted) serum add 5 cm³ of the diphenylamine reagent; this causes a turbidity which disappears at once on being shaken. Stopper the tube, boil for 30 minutes in a water-bath, cool under the tap. For colorimetry, which is proceeded with as quickly as possible, the inulin samples are compared with a standard prepared from $\frac{1}{2}$ cm³ 10 mg% inulin solution + 5 cm³ diphenylamine reagent and heated in a water-bath together with the other inulin samples. This standard covers the interval calculated for undiluted serum from 25 to

150 mg%; if the inulin concentration in plasma lies over 150 mg%, it must be diluted prior to the protein precipitation.

In the case of inulin determination by reduction titration the glucose must be removed from plasma by fermentation prior to hydrolysing the inulin. In the publications cited above, glucose fermentation before inulin hydrolysis is also prescribed for colorimetric inulin determination. However, the chromogenous effect of glucose together with the diphenylamine reagent is only about 2.5 per cent of that of inulin (24), and, apart from the glucose, the chromogenous effect of plasma is very slight. If we put the spontaneous chromogenous effect of plasma as corresponding to 2.5 mg% inulin, it will be seen that it corresponds only to 10 per cent of the lowest concentration of plasma inulin that I can determine. I have therefore omitted the glucose fermentation and for comparator have simply used a serum sample taken prior to the administration of the inulin and treated exactly like the other serum samples; this eliminates the spontaneous chromogenous effect of the plasma. The analysis results given below seem to indicate that this procedure is permissible.

When analysing urine it is diluted to 1: 10 immediately after catheterization to prevent any precipitation of inulin; from this dilutions of 1: 25, 1: 50 and, if required, 1: 100 are prepared. $\frac{1}{2}$ cm³ of each of these dilutions is precipitated with sulphate of zinc and sodium hydroxide and treated exactly as described above for serum. A urine sample taken prior to administering the inulin is used as a control; it should be stated, however, that with these extreme dilutions it has always been clear and colourless.

The following model experiment was performed with this technique:

I. Analyses with pure inulin solutions without precipitation.

Dilutions of 5 mg%, 10 mg%, 15 mg%, 20 mg% and 30 mg% were prepared from a 100 mg% inulin solution. A total of 70 analysis in 5 series were made, each containing 14 samples (the number of tubes capable of standing in the rack). Each series always comprised 3 samples of 10 mg% and also 3 or 2 of the other concentrations. One of the three 10 mg% solutions was used as

Table 1.

Solution concentrations	No. of analyses	Mean values of analysis results	Standard deviations	Coefficients of variations
10 mg %	15	10.00	0.10	1.0 %
5 "	14	5.31	0.23	4.5
15 "	13	14.70	0.23	1.6
20 "	14	19.06	0.57	3.0
30 "	14	28.26	0.60	2.1

a standard, with which all the other samples in the series were compared; the prepared (colourless) reagent was poured into the control tube. The values of the other two 10 mg% solutions were then determined, whereafter a correction was made as illustrated by the following example:

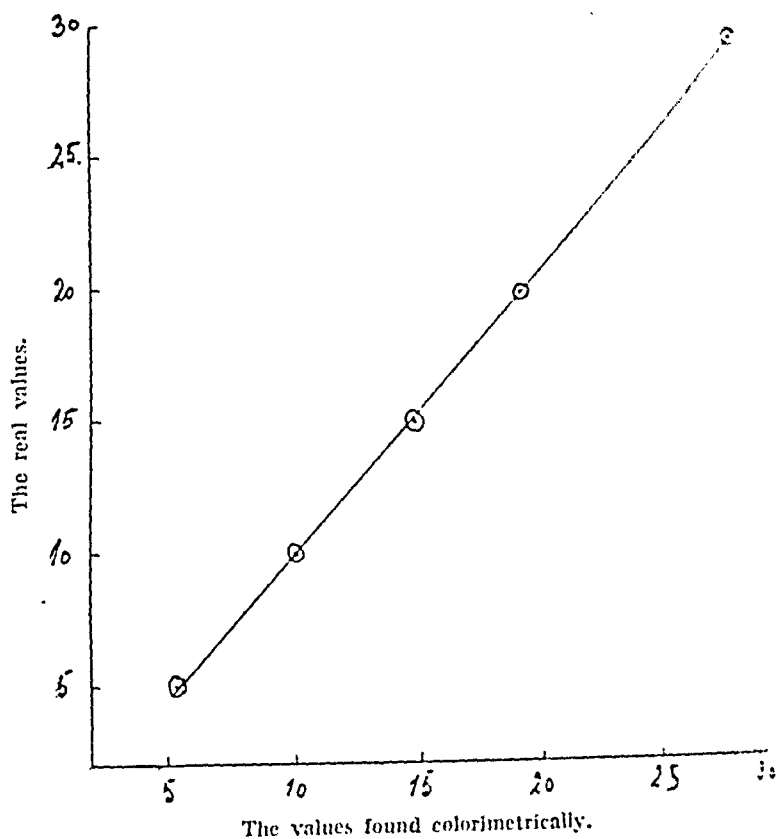
The standard solution is called A and the other two 10 mg% solutions B and C; the values for B and C were found to be e.g. 10.1

and 10.3 mg%. I now assumed that $\frac{A+B+C}{3}$ is probably more

accurately equal to 10 mg% than any one of these values. The sum of A, B and C was found to be 30.4, and therefore each of the three values was corrected by multiplying it by the fraction 30/30.4; thus the true value of A was found to be 9.89, and this was used in the colorimetry of the other solutions in the series. The results appear from Table 1.

As a consequence of making the aforesaid correction the mean value of the values found for the 10 mg% solutions is 10.00. It is of greater interest that the standard deviation is only 0.1, which means that the colorimetry of the solutions which in concentration are near the standard solution is very accurate.

As will appear from the table, I have not found complete proportionality between colour intensity and the inulin concentrations under the experimental conditions chosen, for the values below the standard are too high and those above are too low. If the known concentrations of the solutions are plotted in a coordinate system along the ordinate, and the calculated values along the abscissa, we obtain a number of points which very approximately fall in a straight line. This line passes through the point 10.0—10.0



and in relation to the abscissa has a slope that is slightly steeper than 45° , the tangent to this angle being 1.09. The analyses of blood and urine were corrected by means of this curve.

II. Tests with pure inulin solutions treated with protein precipitation.

The following inulin concentrations were prepared: 25 mg%, 50 mg%, 75 mg%, 100 mg% and 150 mg%. These were treated exactly in accordance with the procedure described for serum.

Table 2 shows the analysis results corrected by the curve described above. It will be seen that the protein precipitation treatment has not affected the inulin content of the samples, which are found to be as complete as the method of analysis permits.

Table 2.

Solution concentrations	No. of analyses	Mean values of analysis results	Standard deviations	Coefficient of variations	Error in mean values
25 mg %	10	25.3	1.1	4.5 %	+ 1.0 %
50 "	7	50.3	1.8	3.5 %	+ 0.6 %
75 "	7	76.1	2.1	4.3 %	+ 1.5 %
100 "	7	98.0	3.2	3.2 %	- 2.0 %
150 "	10	151.1	5.3	3.5 %	+ 0.7 %

III. Tests of serum with varying quantities of inulin.

The method was as follows: to $\frac{1}{2}$ cm³ serum were added $\frac{1}{2}$ cm³ inulin solution, $\frac{1}{2}$ cm³ water, $\frac{1}{2}$ cm³ sulphate of zinc and $\frac{1}{2}$ cm³ sodium hydroxide. The inulin solutions had the following concentrations: 25 mg%, 50 mg%, 75 mg%, 100 mg%, 125 mg% and 150 mg%. Otherwise the procedure was the same as the above. The analyses were made partly with rabbit, partly wit human serum.

Table 3.

Rabbit serum.

Solution concentrations	No. of analyses	Mean values of analysis results	Standard deviations	Coefficient of variations	Error in mean values
25 mg %	14	27.3	2.0	7.5 %	+ 9.2 %
50 "	14	51.2	2.9	5.5 %	+ 2.4 %
75 "	12	73.8	4.1	5.5 %	- 1.6 %
100 "	13	102.6	3.8	3.7 %	+ 2.6 %
125 "	11	127.3	4.3	3.3 %	+ 1.8 %
150 "	14	152.0	4.6	3.0 %	+ 1.3 %
<i>Human serum.</i>					
25 mg %	10	26.3	2.6	9.8 %	+ 5.0 %
50 "	7	51.9	1.6	3.0 %	+ 3.8 %
75 "	7	78.0	3.3	4.3 %	+ 4.0 %
100 "	7	102.0	3.2	3.1 %	+ 2.0 %
125 "	4	125.5	2.8	2.2 %	+ 0.4 %
150 "	4	154.4	2.2	1.6 %	+ 3.1 %

At the low inulin concentrations the variation coefficients and the errors in the mean values, calculated as percentages of the real concentrations, were found to be greatest. This is a natural consequence, partly of the uncertainty of colorimetry with these anything but intense colours, and partly of the fact that the spontaneous chromogenous effect of serum is more marked percentually at the low inulin concentrations. On the whole the results of the analyses seem to present reasonable certainty and accuracy.

The circumstance that the errors of the mean values for both rabbit and human series seem to incline towards the positive might possibly be due to the concentration of serum's water phase as a result of removing the plasma albumin.

IV. Test of rabbit urine with inulin added.

To one part of urine was added one part of an exactly 2 per cent inulin solution. The concentrations of 30 mg%, 20 mg% and 10 mg% were obtained by suitable dilution and precipitation as for serum.

The analysis results (see Table 5) show fairly good accuracy

Table 4.

Concentration of solutions	No. of analyses	Mean values of analysis results	Standard deviations	Coefficients of variations	Errors in mean values
30 mg %	8	30.43	0.60	2.0 %	+ 1.4 %
20 "	8	19.81	0.43	2.2 %	— 1.0 %
10 "	8	10.25	0.18	1.8 %	+ 2.5 %

In two cases I analysed undiluted human urine and found that without the addition of inulin it gives a blue tint corresponding more or less to 10—20 mgr% inulin. As urine when charged with inulin will usually reveal inulin concentrations of over 1 per cent, the spontaneous chromogenous effect of the urine is of no importance, and in fact it is eliminated by using controls.

On Inulin Clearance and the Determination of Inulin in Blood and Urine.

The author reviews the literature on inuline clearance. With great certainty inulin may be proved to pass into the urine by glomerular filtration alone, and is neither reabsorbed nor excreted by the tubules. Inulin clearance is consequently identical with the filtration rate.

The author's method of colorimetric determination of inulin in serum is as follows:

To $\frac{1}{2}$ cm³ serum add 1 cm³ distilled water, shake, add $\frac{1}{2}$ cm³ 10 % ZnSO₄, 7H₂O, shake, add $\frac{1}{2}$ cm³ 0.5 n. NaOH, shake, centrifuge. Dilution: 1/5. $\frac{1}{2}$ cm³ of the supernatant fluid is pipetted into a duran test tube 23 by 115 mm. 5 cm³ of the diphenylamine reagent are added. The tube is closed with a rubber stopper and placed in a rack. The stopper is held in place by a metal plate as shown in fig. 1. The tube is boiled in a water-bath for $\frac{1}{2}$ hour. The colour is compared in a Duboscq colorimeter with a standard prepared from an inulin solution of exactly 10 mg %, of which $\frac{1}{2}$ cm³ is heated with 5 cm³ of the diphenylamine reagent. The read values are sought along the abscissa in fig. 2, and the real values are found correspondingly along the ordinate.

Inulin in urine is determined in exactly the same way after appropriate dilution of the urine.

Preparation of the reagent: *a* stock solution of 10.00 g diphenylamine in 50 cm³ absolute alcohol. *b* 70 cm³ absolute alcohol + 50 cm³ concentrated hydrochloric acid. To 80 cm³ *b* add 5 cm³ of *a*.

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The late prognosis in rheumatic fever.

By

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Appraisal of the prognosis in rheumatic fever is difficult, both because of the great liability to recurrences of the disease and because it as a rule is impossible to say, until some years after an attack, if a cardiac affection is developing. Moreover, the acute attack is, according to some authors, not infrequently followed by secondary arthritis several years later.

In order to get some more light on these questions I have made a follow-up examination of a group of patients who during the years 1921 to 1930 were treated for rheumatic fever in the medical service of the Aarhus Municipal Hospital, either during the first attack or during a recurrence. My object thus became (1) to find out how great the tendency to recurrences was in such a patient-material, (2) to ascertain how many individuals of such a group either had died or were now suffering with some rheumatic cardiac affection, (3) to study the possible connexion between rheumatic fever and chronic affections of the joints.

In making up the material, I began by going critically through all the case records from the above period concerning patients with the diagnoses rheumatic fever and acute or subacute rheumatic polyarthritis, and sorting out from these all the cases which with reasonable certainty could be considered as true rheumatic fever. The cases in which the diagnosis in my opinion was doubtful were

eliminated, and I was particularly watchful against cases with gonorrheal joint-affections¹ and acute articular affections in connexion with an otherwise chronic arthritis. Besides, I eliminated a few, probably true cases of rheumatic fever in which there was a record of concomitant lues, in order that there should not be any doubt about the etiology of such chronic cardiac affections as might be found.

As the result of this scrutiny, I found that the number of patients that had been treated for true rheumatic fever during the period 1921—30 was 215, who thus constitute the material on which the investigation is based. The follow-up was undertaken during the time from October, 1939, to June, 1940; the patients from 1929 and 1930 being examined last, in order to get a minimum observation time of ten years. I succeeded in tracing 209, or 97.2 per cent of the total 215. I tried, as far as possible, to examine them all myself, and where this for some reason or other was impossible, to get reliable information concerning them through other physicians or hospitals; but in about one-fourth of the cases I had to be content with examination by means of a written questionnaire. The general manner in which the examination was undertaken was that I visited the patients in their home, questioned them carefully as regards recurrences, other diseases, symptoms of cardiac affection and as to whether they had any articular lesions; and finally I made a stethoscopic examination, which, however, in a couple of cases was refused. The stethoscopy of the heart was in practically all cases made with the patient both in sitting (standing) and recumbent posture, in left lateral recumbent position and after efforts. Finally, I examined the function and condition of the joints. In all suspect cases I asked the patient to come to the hospital for further examination, where I then took their blood pressure and electrocardiogram and a roentgenograph of the heart.

Both sexes and all age-classes are represented in the material. Table I shows the age at first attack and distribution by sex.

As the table shows, about two-thirds of the patients had their first attack before the age of twenty, and the incidence rate was highest, by far, between the ages of eleven and fifteen years. The age distribution is seen more clearly, still, from Chart I, which

¹ Gonococcus reaction test (which dates only from the latter part of 1928) was performed only on a few of the patients from 1930.

Table I.

Incidence of first Attacks and Distribution by Sex of the 215 Patients treated for Rheumatic Fever during the Period 1921—1930.

Age	Male	Female	Total	Incidence rate (per cent)
0—5	2	6	8	3.6
6—10	21	14	35	16.2
11—15	27	31	58	27.0
16—20	17	16	33	15.3
21—25	6	20	26	12.1
26—30	2	21	23	10.7
31—35	5	5	10	4.6
36—40	6	8	14	6.5
41—45	0	2	2	0.9
46—50	2	3	5	2.3
51—55	0	0	0	0
56—60	0	1	1	0.4
	88 = 40.9 per cent	127 = 59.1 per cent	215	100

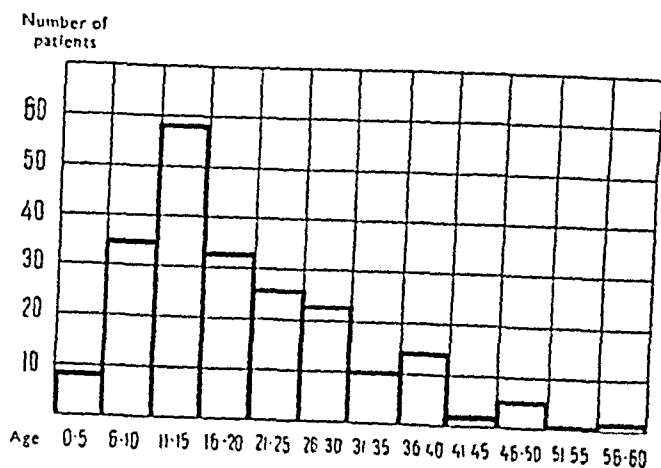


Chart I.

Incidence of first attacks by age groups.

shows the incidence for each five-year age group. The curve strikingly illustrates the preponderant incidence of first attacks in childhood, especially in the age group 11—15 years.

Chart II shows, in similar arrangement, the distribution both by age and by sex under the different age groups. We see that the distribution by sex is practically the same in all the five-year

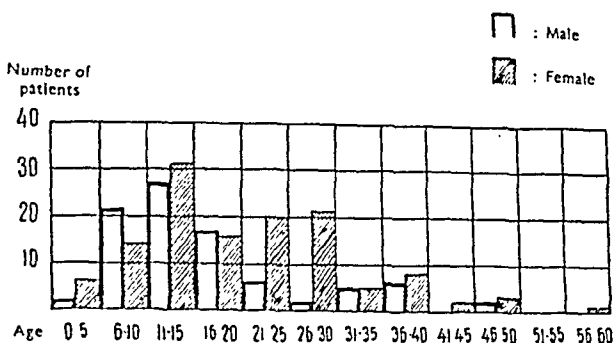


Chart II.

Incidence of first attacks by age groups and sex.

groups, except in the groups 21—25 and 26—30, where the »female» columns greatly overtop the »male».

The age distribution of first attacks has been investigated, on large mixed materials, both by Mackie (New York) and by Edstrom (Sweden). Their findings are shown, together with my own, in Chart III.

As the Chart shows, there is almost complete accordance between Mackie's findings and my own, and Edstrom's patients were only slightly older. Further the curves show that initial attacks before the fifth and after the fortieth year of age were rare in all the three materials.

Finally must be mentioned a comprehensive Danish investigation in the middle of the last century, by Lange, who among 994

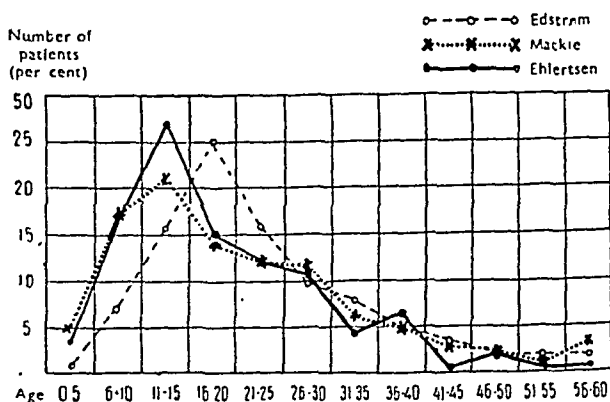


Chart III.

Curves showing incidence rates of first attacks in three different materials.

individuals with first attack found a gradual rise of the incidence curve until the twentieth year of age, whereupon the number of cases remained fairly constant until the twenty-fifth year, after which period the curve again showed an even, gradual fall.

Also the distribution between the two sexes is seen from Table I and Chart II. There is a marked predominance of females, 59.1 per cent as compared with 40.9 per cent males. This does not however apply to the ages under twenty, where the numerical distribution is exactly equal, 67 cases of each sex. As already mentioned, the predominance of females is particularly marked in the age group 21—30, which has 41 females and only 8 males. After the thirtieth year of age the distribution is again approximately equal. An explanation of this may perhaps be found — as also Freund suggests — in the circumstance that young married women with small children cannot very well be taken care of at home, whereas men as a rule can better go through an attack of rheumatic fever without hospitalisation. Another possible explanation is that some of these women may have had gonorrheal polyarthritis, after all. At least, it has been shown by Warburg that there during the period with which we are concerned in the present investigation was a great increase of female gonorrhea, and therefore probably also of gonorrheal polyarthritis. And yet, if we look at the distribution, by sex, of rheumatic fever cases among individuals between the ages of twenty-one and thirty during the period 1939—41, the fact that of a total of 47 patients treated for true rheumatic fever during these three years 13 were between those ages, and that, of these thirteen, 10 were females and only 3 males, seems to be strongly indicative of a real preponderance of females of that age group in the hospital materials.

Most of the statements in the literature point to an equal distribution between the two sexes. In that respect there is no marked difference between the reports from the different countries. Thus, Mackie found 49.6 per cent of females among 393, Edstrom 52.2 per cent among 862, and Lange 51 per cent among 991. On the basis of statistics for the period 1911—20, respecting the distribution, by sex, of patients with rheumatic fever in all the Swedish hospitals, Edstrom also expresses the belief that the distribution often corresponds very closely to the proportion between the two sexes in the population of the region in question.

The tendency to recurrences.

A. Earlier Investigations.

The tendency for rheumatic fever to recur is very variable. Some individuals will have only one recurrence, others two or three, a few up to as many as half a dozen. Mackie found that of a series of 252 cases representing patients of both sexes and all ages 71 per cent had at least one recurrence. The percentage of recurrences was highest among the young; in the group of 165 individuals under the age of twenty 78.2 per cent had at least one return of acute rheumatic fever, whereas only 58.6 per cent of 87 cases above that age had recurrences. He also separates these cases into five-year age groups according to the age at first attack and shows that those cases which occurred between the fifth and tenth year had the highest rate of recurrences, namely 93 per cent. In the later age groups the incidence curve followed a steady downward course, but it was not until after the age of thirty years that the incidence fell below 50 per cent. It does not seem that any age is exempt from the possibility of recurrence.

Mackie's attempts to ascertain the average time interval between the initial attack and the first recurrence revealed the fact that only 57 per cent had the first recurrence within four years after the primary episode. In 144 cases he found it possible to ascertain exactly the length of time that elapsed between the initial attack and the first recurrence. In 23.6 per cent the recurrence occurred within one year, in 38.8 per cent within two years, in 57 per cent within four years, while in the remaining 43 per cent it was four years or longer before the secondary attack of acute rheumatism occurred. It does not clearly appear, however, from his report how long an observation time he has had. He further selected from his material 65 cases, which he observed over a period of several years. A large number of these individuals had had recurrences ten years after the initial attack, a few showed recurrences after fifteen to twenty-five years, and in four acute rheumatism reappeared after more than thirty years. Two of the latter had several recurrences, however; one after six, sixteen and thirty-eight years, the other after eleven and thirty-one years. Mackie says that these data »almost inevitably lead one to the conviction that rheumatic

fever cannot be regarded as an acute affection terminating after a longer or shorter interval. It is probably incorrect to regard the secondary attacks as a simple reinfection. The concept of rheumatism as a chronic, slowly progressing disease characterised by intervals of calm simulating recovery, and periods of activity which entail further damage to the organism, seems more accurately to correspond with observed phenomena.»

Kaiser (Rochester, N. Y.) found recurrences within three years of the initial attack in 49 per cent of a series of 564 children. Among a smaller number, who were followed for three to five years, there were recurrences, during that period, in 40 per cent, and among 200 who were followed for five to ten years the disease recurred in 25 per cent.

Wilson, Lingg and Crawford (New York) found recurrences in 73 per cent of a series of 413 children, though not all of them had been followed for three years. Half of these recurrences occurred within the first year, only 15 per cent of them after four years.

Also Roth, Lingg and Whittemore (New York City) report on a child series, comprising 488 cases observed over a period of eight years. Of these, 68 per cent had one recurrence, 40 per cent two or more. Seventy-three per cent of the recurrences manifested themselves within three years of the first attack.

According to Coombs (England), recurrences are frequent especially in the first ten to fifteen years after the primary episode.

Glover (England) thinks that rheumatic fever in a great many cases, perhaps in 70 per cent, takes the form of a chronic infection, which may have long periods of latency alternating with periods of activity and progression.

Anton Fischer (Berlin) gives the percentage of recurrences as about 35 for adults and about 50 for children.

Edstrom (Lund, Sweden) found recurrences in 50 per cent of his large, mixed material of 694 patients observed over periods of from one to twenty-four years. In 25 per cent the disease recurred more than once. He found the tendency to recurrences greatest, 97 per cent, among those who had had their first attack between the fourth and tenth year of age, whereupon there was a steady, gradual fall of the incidence rate with increasing age. More than one-fourth of all the recurrences occurred within one year of the initial attack. In 6 per cent of all those who had a return of the acute

phenomena, there was however a lapse of over ten years before the secondary attack occurred. The longest interval between first attack and first recurrence observed by Edstrom was forty-one years. From all these data he concludes that while the probability of recurrence and the chance of escaping a second attack are about even during the first ten years after the initial episode, the risk is only as 1 to 16 if there has been complete freedom from symptoms during those ten years.

B. Own Results.

Most of the recurrences occurred within a year after the initial infection, but in not a few cases the first secondary attack did not occur until between ten and twenty years after the first, and a few got their first recurrence only after a still longer interval. Three cases will illustrate this. The first patient had his initial attack at the age of six and got a recurrence twenty-seven years after. The second had bouts of rheumatic fever in his eleventh and twelfth year, then there was a lapse of twenty-four years before the next recurrence set in, and two years after that the disease recurred a third time. The third patient had rheumatic fever for the first time at the age of twenty-three and his only recurrence twenty-three years later.

In Table II all the followed-up cases are separated into five-year age groups according to the age of the patient at the time of the first attack; and the number who had recurrences, and how many of these, is set down for each group. Further the Table shows the incidence per cent for the five youngest groups, but not for the older, because the figures for these are very small. It is seen that the liability to recurrences is greatest for the youngest, and seems to become gradually less with increasing age at first attack. This will be still clearer from Chart IV, which shows the incidence curve for my own findings, together with that of Edstrom's for comparison.

As already pointed out, the time interval between the initial infection and the first recurrence can vary within very wide limits. This will be seen from Table III, where the recurring cases are set down by age groups and the number of years elapsed before the secondary attack stated for each group.

Table II.

Incidence of Recurrence among the 209 followed-up Patients distributed into five-year groups according to the age at the time of first attack.

Age at first attack	Total cases	No recurrence	Total with recurrences	1 recurrence	2 recurrences	3 recurrences	4 recurrences or more	Incidence (per cent)
0—5	8	0	8	2	4	2		100
6—10	35	8	27	10	10	4	3	77
11—15	57	31	26	15	6	3	2	45
16—20	32	19	13	8	3	2		40
21—25	24	16	8	6	1	1		33
26—30	21	13	8	5	3			
31—35	10	4	6	3	3			
36—40	14	7	7	5		2		
41—45	2	2	0					
46—50	5	4	1		1			
51—55	0							
56—60	1	1	0					
Total	209	105	104	54	31	14	5	
Per Cent ..	(100)	50.3	49.7	26	15	7	2	

24 per cent
more than one recurrence

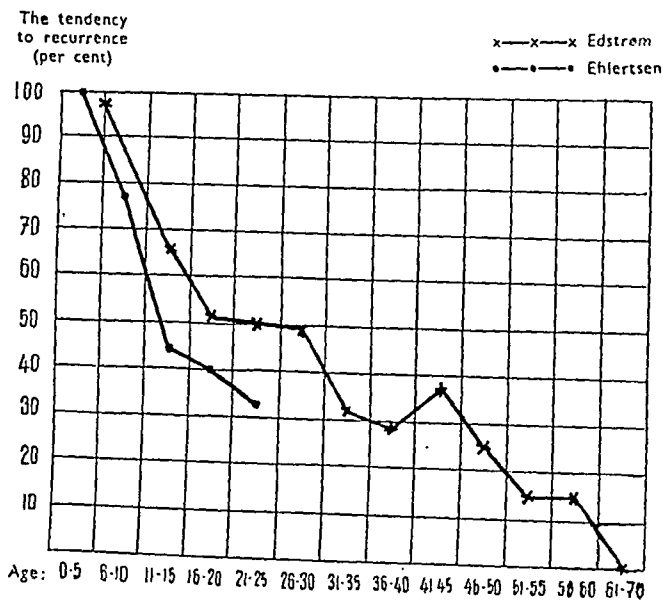


Chart IV.

Two curves showing the incidence of recurrences, per cent, in the different age groups in Edstrom's and the author's materials.

Table III.

Time Interval between primary Infection and first Recurrence in
104 Cases.

Age at time of first attack	Interval (years)							
	0—1	1—2	2—3	3—4	4—5	5—10	10—20	over 20
0—5.....			1	2	1	3	1	
6—10.....		4	6	2	2	10	1	2
11—15.....	2	5	6	2	3	3	5	
16—20.....		3		1	3	2	4	
21—25.....		1	2			1	3	1
26—30.....	2		1		2	2	1	
31—35.....			2			4		
36—40.....			1		2	1	3	
41—45.....								
46—50.....						1		
Total	4	13	19	7	13	27	18	3

83 = 80 per cent of the recurring.

We thus see that the disease may recur at almost any time after the first attack. It is true that 80 per cent of the recurrences registered up to the termination of the observation period had occurred within ten years after the primary episode, but as many as nearly 20 per cent did not occur until after an interval of between ten and twenty years, and three, as already mentioned, not until after an even longer lapse of time.

The result of my investigations is that of a mixed material representing both sexes and all age classes about one half get at least one return of acute rheumatic fever; that the secondary attack may occur at almost any time after the primary episode, from less than one to more than twenty years after the latter (maximum interval in my material: twenty-seven years); that, in other words, there is no certainty, at any time, against the possibility of recurrences, though it is true that most of these, by far, (in my material 80 per cent) occur within ten years; and, finally, that in about half of the recurrent cases there is only one, in the other half two or more returns of the disease.

The frequency of rheumatic heart disease.

A. Earlier Investigations.

In Sweden, Edstrom made in 1935 an extensive follow-up examination of patients with a past history of rheumatic fever. He collected a material of not less than about 850 cases, comprising all those that had been treated for that disease in the hospitals of Malmohus county, in Lund, during the period 1911—33. With exception of 155 (18 per cent), who could not be traced, these were examined during 1934 to 1935, thus giving an observation time of from one to twenty-four years. The material comprised patients of both sexes and all age classes. Edstrom found that 419 of 694 (60 per cent) had got a still existing, organic heart disease or had died with such a lesion. Of these, he lists 177, however, with the diagnosis of mitral insufficiency, — a diagnosis which by many clinicians is considered as highly problematical, and which I have not used in my material. If we therefore deduct these 177 from the 419, we get a total of 242 of 694, or 35 per cent, with organic heart disease.

Coombs (1924) followed for a number of years a child series of 253 with positive cardiac affections from the start and another series of 121 with uncertain cardiac symptoms. The average age at the time of first attack was 10.2 years; the average age at which they were first seen by him was 11.8 years. In the first series — that with positive cardiac affections — 5.1 per cent died of rheumatic heart disease within one year after the onset, 11.2 per cent within the first five years, 21.4 per cent within the first ten years. He points out the great mortality in the first year after the onset in this series, in contrast to the series with uncertain cardiac symptoms. Of the latter, 12 could not be traced, of the remaining 109 none died during the first year, of 95 followed until the fifth year only one had died, of 79 followed till the tenth year five had died.

According to this, about two-thirds of the series with positive signs of heart disease at the start and about one-half of the series with uncertain signs should get a lasting rheumatic, cardiac lesion. The expected incidence of chronic cardiac involvement in a series with neither certain nor uncertain signs of carditis cannot be seen.

	Of 100 patients with sure signs of cardiac affection when first seen	Of 100 patients, including those whose signs were uncertain
Recovered	31	44
Died at/before the 20th year.....	27—28	19
» » » 30th »	37—38	28
» » » 40th »	50	39
Alive, but invalids, 40 years after the onset of the disease	19	17

Coombs's figures have been simplified by Warburg, who assumes that half of the patients escape permanent cardiac complications. He calculates that 10 per cent die before the twentieth year of the disease, 20 per cent before the thirtieth and 30 per cent before the fortieth year; that 10 per cent survive the fortieth year suffering with heart disease, while 60 per cent either do not get chronic heart disease or recover. Warburg thus believes, from Coombs's figures, that about 40 per cent get heart disease.

Bland and Jones (1939) followed children with rheumatic infection from the House of the Good Samaritan in Boston for a number of years. Among them there is a series of 314, the average age of whom was eight years, who after they had recovered from the initial rheumatic infection had no recognisable heart lesion. This series was observed for ten years, and eventually 79, or about one-fourth of the whole number, showed signs of permanent valvular lesion. One hundred and thirty-two of the 314 had no recurrences, and only 6 per cent of these showed signs of valvular deformity; the other 182 had repeated recurrences, and 39 per cent of them developed valvular affections. The results of the examination of the seventy-nine with positive rheumatic heart disease following the first attack have not yet been published, — or at least they have not reached Denmark at the time of the present writing, — but in an account of a discussion on the subject one of the authors is reported as having stated that 60 per cent are to-day leading normal lives, and that of the others 25 per cent have died, while 15 per cent are still alive, but with moderate or severe cardiac affections.

A similar investigation has been carried out by Boone and Levine

(1938). Their material was a series of 225 children (average age, 13.8 years) with past rheumatic infection, but in whom cardiac stethoscopy at the first examination revealed nothing abnormal, or at most a systolic murmur. The average observation time was 9.6 years. At the first examination, potential heart disease was diagnosed in 166, mitral insufficiency in 59. By the end of the observation period 4.8 per cent of the first group had developed permanent valvular lesions, while such lesions were found in as many as 42 per cent of the last group. From this, the authors conclude that patients with potential heart disease after a single attack of rheumatic fever have a 96 per cent chance of escaping valvular trouble before the fifth year, and that after that time the chance against such a complication is 100 per cent. Of the group with mitral insufficiency, 19 per cent of those who had only had one attack of rheumatic fever got permanent valvular disease, against 61 per cent of those who had several attacks. Patients with mitral insufficiency have an 81 per cent chance of escaping further valvular lesion before five years, and a 100 per cent chance after that lapse of time if they have had only one attack of reumatic fever; if they have had several, the chance is in the first five years only 39 per cent, but for the following twenty years the prognosis gets better and better. If we look at the mitral insufficiency as merely a potential rheumatic heart disease and consider the two groups together, the result is about 15 per cent with chronic valvular lesions.

Mackie (48) followed 204 patients — of a series of 366 of both sexes and all ages — who during the initial attack showed signs of cardiac involvement. The observation time is only stated as «varying, with a minimum of four months». Of these two hundred and four, 42 (21 per cent) showed decided improvement, while 57 (28 per cent) got worse and the remainder showed no change. These figures do not tell one very much, because it isn't clear for how long the cases were observed; but that it, as already said, must have been for a considerable length of time is seen from Mackie's mention of 25 patients whom he followed, and who all got mitral stenosis. In 22 of these the signs of this deformity became established within two years, in the 3 others not until after five to six and a half years.

Bartram (1925) tells about 141 children treated for rheumatic infection during the years 1916 to 1921. One hundred and seven of

them had some cardiac lesion or other during their stay. In 1923, 28 of these had died, 9 were cardiac invalids, 57 were leading moderately active lives and only 13 were entirely well. Considering the short observation time this is an exceedingly bad prognosis.

Walsh, Bland and Jones (1940) made a special study of a group of 81 children and young people with pure mitral stenosis, out of more than 1,700 treated for rheumatic fever at the House of the Good Samaritan in Boston. All cases in which the stenosis was combined with insufficiency or aortic deformity were excluded. The average age at which the initial attack of rheumatic fever began was 9.3 years. In 48 of the group the sure physical signs of the mitral stenosis made their appearance during the period of observation. In 27 of these there were auscultatory signs of valvular disease from the onset, but no sure signs of involvement of the mitral valve, whereas there in the other 21 was no evidence of cardiac involvement after their recovery from the initial rheumatic fever. The first evidence of valvular affection in the twenty-one patients of this subgroup was in two of them a systolic murmur at the cardiac apex, which slowly progressed to systolic and diastolic murmurs. In 3 others the latter combination appeared as the first indication, followed later, over a period of years, by a diminution of the systolic murmur, until this ultimately disappeared as the systolic murmur and the first heart sound acquired the characteristics of pure mitral stenosis. In contrast to this, the first sign in the remaining 16 was a short mid-diastolic murmur following a rather prominent third heart sound. This murmur later evolved into a crescendo presystolic murmur, without the occurrence at any stage of systolic murmurs. In 5 of all the forty-eight patients with pure mitral stenosis the signs of that condition were established in the first five year period, in 27 they developed within six to ten years, in the remaining 16 not until after ten years (in 4 of the latter after sixteen to twenty, in 2 after twenty to twenty-four years). In the entire series of 81, the initial rheumatic infection was characterised by a very mild course, and the same was the case with the recrudescences, which occurred in 85 per cent of the patients. Clinically recognisable cardiac involvement during the initial attack was present in only 57 per cent, whereas the experience of Walsh and his associates with the large group of 1,700 patients indicated an initial involvement of the heart in about 70 per cent. After ten years 53 (65 per cent) of the eighty-

one were able to lead normal lives, 13 (16 per cent) were slightly limited, 4 (5 per cent) were moderately limited by functional dyspnea and 11 (13 per cent) had died. The authors emphasise the contrast of this low death rate to a death rate of 24 per cent for a control group of 1,000 rheumatic patients observed by them for the same length of time.

Walsh and his associates ascribe the favorable course of the disease to the fact that the initial rheumatic fever on the basis of which it developed in these patients was very mild; a circumstance which they believe favored the continued integrity of the myocardium.

But the diagnosis of a rheumatic fever does not in itself contain any indication of the subsequent course of the disease, which, according to some authors, depends on the type of the eventual cardiac lesion. Though my object with the present study has not been to investigate the course of the rheumatic cardiac disease, I therefore find it natural briefly to consider also this question.

As Warburg has pointed out, all the valvular lesions in this disease are sinistral. It is extremely rare to find lesions of the tricuspid or of the pulmonary valve without involvement of the mitral; and if the mitral deformity is manifest, the diagnosticated presence also of a tricuspidal lesion does not alter the prognosis (Warburg). The three types that are of interest are thus mitral stenosis, mitral stenosis coupled with lesion of the aortic valve, and lesions of the latter.

As regards the incidence rate of each of these types, the statements in the literature are fairly accordant. Thus, De Graff and Lingo found among 694 cases mitral stenosis in 62 per cent, mitral and aortic lesions in 33 per cent and lesion only of the aortic valve in 1.2 per cent. The authors themselves think that many cases of the last named type may have been counted among the combined lesions owing to the presence of a Flint sound. Willius found, among 160 patients who died of cardiac disease, mitral stenosis in 77.4 per cent, mitral and aortic lesions in 14 per cent, aortic lesion only in 14 per cent; Hart, Wood & Daughton, among 138 cases, mitral stenosis in 58 per cent, mitral and aortic lesions in 28 per cent, aortic lesion only in 13 per cent; Simmons, among 206 cases, mitral stenosis in 83 per cent, mitral and aortic lesions in 11.3 per cent, aortic lesion only in

5.7 per cent. Edstrom had among 153 patients with valvular affections of these types 62 per cent with mitral stenosis, 22 per cent with mitral and aortic lesions and 16 per cent with only aortic lesion; Aastrup, among 131 cases, 69 per cent with mitral stenosis, 17 per cent with mitral and aortic lesions, 14 per cent with only aortic lesion. We thus see that mitral stenosis is by far the commonest type, with the combined lesions second in frequency and the isolated aortic lesion the uncommonest.

The types occur with different frequency in the two sexes. The incidence of mitral stenosis is highest, by far, in women. White finds the ratio of females to males in this respect to be as 3 to 2; Aastrup finds the same (54:36), and Cabot's necropsy statistics give the ratio as 62:45. As regards aortic lesions, the condition is the reverse, with even greater preponderance for the males. Of Cabot's 28 patients with aortic stenosis, 25 were men; among Aastrup's 19 with defects of the aortic valve there was only one woman.

As to whether the prognosis depends upon the type of the valvular lesion, the authors are, as already said, at variance. Of Cabot's patients with mitral stenosis, 30 per cent got over fifty years old, and the same was the case with 35 per cent of those with both mitral and aortic lesions and 50 per cent of those with lesions only of the aortic valve. He further found that the average persistence of the symptoms was 15 years for those with mitral stenosis, 3 years for those with both mitral and aortic lesions. Willius found the average age at death, for a series of 124 patients with mitral stenosis, to be thirty years, the average duration of life from the initial infection twelve years. The corresponding figures were for 15 patients with both mitral and aortic lesions thirty-two and sixteen years, for 21 with only aortic lesion forty-three and twenty-two years. De Graff and Lingg, on the other hand, found the average length of time that the patients survived to be more or less the same irrespective of the type of the lesion, namely between sixteen and seventeen years. Aastrup found the average age at death for the patients with mitral stenosis to be forty-three years, the average time from the the first rheumatic manifestation to death twenty-three years. For those with both mitral and aortic lesions his figures are forty-five and twenty-seven years, for those with only aortic lesion fifty-five and twenty-nine years. The difference is thus not very great; the only type with which the patients

undoubtedly live longer is the aortic stenosis, of which Cabot speaks as «a lesion of elderly men, but when women have it (which is rare) they live even longer than men.» This fact is of particular interest in connexion with the present study, because it is possible that a number of these cases in spite of the rather long observation time were not recognised at the follow-up examination, owing to the clinical signs not having developed yet. It may therefore be of interest to go a little more deeply into this matter, all the more because it is with regard to the aortic affections that the etiologic diagnosis is particularly difficult.

In some cases the cusps of the aortic valve are on necropsy found strongly calcified, thickened and grown together, and at the same time there will usually be marked stenosis of the orifice, while the heart otherwise, except for pronounced hypertrophy, shows no particular changes. Of the etiology of this affection there are different opinions. Moenckeberg described it, in 1904, as «primary sclerosis of the aortic cusps». He did not think that the process in the valve was different from the one found in the intima of the aorta in cases of senile arteriosclerosis, and he believed that it could develop entirely independently of any inflammatory processes. In 1926, Clawson, Bell and Hartzell wrote that while it is true that this type of lesion can develop independently of such processes its frequent association with known inflammatory lesions such as, for instance, Aschoff bodies in the myocardium, makes the etiology uncertain. These authors termed the process «the calcified nodular aortic valve deformity.» In a later paper (1931) they showed that the etiology often is rheumatic. In 40 per cent of a series of 93 cases of the type they found rheumatic infection in the anamnesis. In 1938 and 1940, Clawson, Noble and Lufkin published further material to elucidation of the etiology of the disease. They point out that calcification of deformed valves, especially of the mitral valve, is a common finding, but they do not think that atherosclerotic changes in the valves are ever great enough to produce stenosis or insufficiency of a degree liable to be the cause of cardiac insufficiency.

Also Christian considers these aortic lesions as rheumatic. In 11 of a series of 21 patients he found rheumatic fever in the anamnesis as far as from thirteen to forty-eight years back. Boas, McGinn & White and Contratto & Levine are of the same opinion.

Margolis, Ziellesen & Barnes do not think that the etiology can be determined with certainty; Libman and Sohval & Gross rather agree with the views of Moenckeberg.

Christian holds the affection for a clinically distinct entity with the following characteristics. 1) Occurrence chiefly in men and relatively late in life; 2) progression slow and incompensation tardy; 3) systolic fremitus and murmur over the aorta, often accompanied by a diastolic murmur; 4) considerable hypertrophy of the heart; 5) often characteristic plateau pulse and normal or reduced pulse pressure; 6) nothing in the last half of life that sheds light on the etiology; 7) heart, on necropsy, very much enlarged, the aortic valves very much narrowed, thickened and often adherent to each other and strongly calcified, while the other valves are normal; 8) frequently rheumatic fever in the anamnesis; 9) sometimes roentgenologically demonstrable calcification of the aortic valves.

As regards the sex incidence, all the materials show a preponderance of males:

A u t h o r	Total number of cases	Male	Female
McGinn and White.....	86	69	17
Christian	21	15	6
Cabot	28	25	3
Margolis et al.....	42	34	8
Clawson et al.....	200	165	35
Contratto and Levine	180	108	72

All the materials likewise show the highest age incidence for the relatively old age groups:

McGinn and White.... 60 per cent over 50 years old.
 Christian (21 cases).... 13 over 50 years old (7 of these over 60).
 Cabot (28 »).... 15 » 50 » » and 7 over 70.
 Margolis (42 »).... 35 » 50 » »
 Clawson 75 per cent over 50 years old.
 Contratto and Levine .. all ages from 13 to 81 represented; most of them in the sixth decade of life.

As regards the frequency of the disease, McGinn and White state that it was found in 123 (1.8 per cent) of 6,800 postmortem cases of all diseases and in 113 (2.3 per cent) of 4,800 clinical heart patients.

B. Own Investigations.

Of the 209 followed-up patients, 35 (16.7 per cent) had chronic rheumatic heart disease or had died of a chronic affection of that nature. The incidence of the various types is shown in Table IV.

As the Table shows, valvular lesion, especially mitral stenosis, was the most frequent finding (15 of the 35). In three cases the diagnosis was pancarditis. This diagnosis was made when it was impossible to determine the type of the cardiac lesion more precisely.

One of these patients was a girl, seven years old, who during the acute attack had pronounced myocarditis with great distension of the heart. Six months afterwards she got scarlet fever, and a month after she had recovered from that she died. The second was a woman, forty-two years old, who had had rheumatic fever twice before, when she was twenty-six and when she was thirty-two. A week before she was admitted she got shifting pains in the joints and a temperature of 39° C. During her stay in the hospital she had continued attacks of such pains and temperature about 40° C; besides, she complained of pain in the precordium. Stethoscopy of the heart showed nothing abnormal (no electrocardiogram or roentgenograph was taken). A week after admission she died. Perhaps her case should rather be considered as a hyperpyretic form of the disease. The third of the three patients was a man, thirty-eight years old, who had had rheumatic fever twice before, when he was eighteen and when he was thirty-two. Prior to his admission he had been feeling tired and run down, with dyspnea and palpitation. During his stay in the hospital he showed symptoms of cardiac insufficiency, no signs of valvular lesion, but there were pericardiac friction sounds and on the electrocardiogram auricular flutter with shifting block. After three-four weeks he died from cardiac insufficiency.

One case is listed with the diagnosis acute endocarditis during chronic state. The patient was a woman, twenty-three years old, who died of cerebral embolism. Perhaps the case was one of subacute bacterial endocarditis.

She had had rheumatic fever at the age of twelve, and again at the age of twenty. Cardiac stethoscopy during her last attack had showed ictus in I C₆ in the anterior axillary line, systolic murmur at the apex, systolic and diastolic murmur over the rest of the precordium. The pulse had been rapid and there was nail pulse. Three years after, she was admitted to the hospital. Until two weeks before she had been well, but then she suddenly declined and her temperature became high. Examination showed nothing abnormal except extension of the heart limits. Three weeks after her entrance she died after a hemiplegia. There was no necropsy.

Table IV.

Total Cases of chronic, rheumatic Heart Disease in the entire Material.

	Total	Female	Male
Treated for rheumatic fever in the Aarhus Municipal Hospital during the period 1921—30	215	127	88
Followed up and examined between Oct. 1939 and June 1940	209	121	88
Number of the followed in whom rheumatic cardiac lesions were found (including those who had died during the period)	35 (16.7 per cent)	24 (19.9 per cent)	11 (12.5 per cent)
Type of disease:			
Mitral stenosis	9	8	1
Mitral stenosis + aortic lesion	3	2	1
Pericarditis	2	2	0
Pancarditis	3	2	1
Acute endocarditis in chron.	1	1	0
Observed for rheumatic heart disease	8	4	4
Possibly rheumatic heart disease	6	4	2
	35	24	11

The group of 8 patients listed as »observed for rheumatic heart disease» comprises individuals in whom no sure signs of such a disease could be found, but in whom it was strongly suspected either from the stethoscopic picture coupled with the fact that they had had rheumatic fever within the past six years or on account of the roentgenologic findings or the electrocardiogram. They had all had their first attack as children, and most of them had had at least one recurrence. Most of them complained of vague cardiac symp-

toms, which did not cause them any particular discomfort, however, and their condition at the time of the examination was thus in all cases good. In a few there were slight irregularities in the roentgenologic picture, and in two of them there was prolonged P—R in the electrocardiographic tracings. Only in a few of them was there under stethoscopy heard a systolic murmur. Finally, four of them had had a recurrence within the last five years. On account of these findings and considering that they were all young (between twenty and thirty-two years) at the time of the examination, I felt justified in considering them as very liable to get rheumatic heart disease.

The last group in the Table, listed with the designation »possibly rheumatic heart disease», comprises 6 patients who could only be examined by questionnaire. They all in their replies complained of symptoms which might be interpreted as indicative of possible cardiac affection, and two of them had had symptoms of heart disease during their stay in the hospital.

As it may be seen from the Table (Table IV), I did not find in any of the patients any aortic lesion of the calcified type mentioned some pages back. In order to find out something about the frequency of this lesion and about possible rheumatic fever in the history of such patients, I made a search through the postmortem journals of the Pathoanatomical Institute of the Aarhus Municipal Hospital, from as far back as the beginning of 1924 up to, and including, the month of January, 1941. Among the 4,000 postmortem examinations carried out during this period, I found, in all, 24 cases of isolated aortic stenosis of the type described, but only in connexion with 4 of these was there any record of past rheumatic fever. In 15 of the others the cardiac affection had not been recognised clinically, in 5 the clinical diagnosis was chronic heart disease, only in 4 had the stenosis been clinically diagnosed. Of the twenty-four patients, 15 were men, 9 women. The average age at death was for all the 24 sixty years, for the men sixty-three years, for the women fifty-eight. The youngest was thirty-four, the oldest ninety-two, but only 4 of them all under fifty years old at the time of death.

It has not been possible on the basis of this material to contribute essentially to the clinical picture of this type of aortic lesion, nor to throw any light on the question of now often it may be due to rheumatic fever. This is in the first place because the journals, especially the older ones, are rather summary, and because many of

Table V.

Frequency Distribution of Heart Disease according to Age at first Attack of rheumatic Fever.

Age at first Attack of Rheumatic Fever		Number with Heart Disease
Under 15 years:	Male 50	9 (18 per cent)
	Female 50	16 (32 " ")
	Total 100	25 (25 " ")
Over 15 years:	Male 38	2 (5.3 per cent)
	Female 71	8 (11.2 " ")
	Total 109	10 (9.2 " ")

the patients at the time of their admission were already in a moribund state; but, besides, the condition of the heart was in 15 of the 24 cases paid no attention to, at all, because most of these patients died following a surgical operation.

If we separate the material into two groups according to whether the first attack of rheumatic fever occurred before or after the fifteenth year of life (Table V), we find that the liability to cardiac involvement is three times greater for the younger group than for the older.

As the Table shows, 100 of the examined had had their first attack before the age of fifteen, and 25 per cent of these had heart disease, whereas this was the case only with 10, or 9.2 per cent, of those who had had their first attack after that age. The Table further shows that in the younger group the sex incidence is entirely equal, but there are about twice as many women as men with heart disease (respectively 32 and 18 per cent). Also in the older group there are more women than men with heart disease, but the figures are here so small that no conclusions can be drawn from them.

My investigation thus seems to show that the liability to get heart disease is three times greater for those who have had a first attack of rheumatic fever before the age of fifteen than for those who have had such a first attack after that age; and that this liability to cardiac involvement is particularly great in the case of the women, one-third of whom in that age group of my material had heart disease. Of the 209 patients in my series, 12 (5.7 per cent)

died as result of the rheumatic infection, between one and fifty-two years after the initial attack. Only 3 (1.4 per cent of the entire series) died within five years, only 4 (1.9 per cent) within ten years, after the first attack.

The Diagnosis of cardiac Affections during the acute Attack.

Among the 209 followed-up cases there were, as described, 35 patients with rheumatic heart disease, while 13 had died from other causes and 7 had cardiac affections not due to rheumatism. This makes a total of 55 either alive with heart disease or dead. The remaining 154 were all found sound of heart.

Of these one hundred and fifty-four there were 56 whose cases during their stay in the hospital had been variously diagnosed as chronic heart disease, mitral deformity or endocarditis. As a rule, these diagnoses were based on the presence of a systolic murmur and accentuated P_2 , in a few cases on a presystolic murmur and in some cases on a stethoscopically demonstrated extension of the heart limits. All these patients were at the after-examination found sound of heart. Thirty-six of them I examined stethoscopically and found only in a few of them a slight apical systolic murmur. Of 11 there were further taken roentgenographs and electrograms, but nothing abnormal found. About the remaining 20 I have only the information contained in their replies to my questionnaires, but they all declare themselves well and in possession of their full capacity for work. Among those whom I examined stethoscopically were also two of those in whom presystolic murmur had been established during their stay in the hospital. This murmur had now disappeared and they, too, were well.

Bland, White and Jones (1935) mention similar findings. Among a series of 950 patients with rheumatic heart lesion they found in 32, during the acute rheumatic infection, dilatation and diastolic murmur, which were ascribed to mitral stenosis. Eight years later all the thirty-two had normal hearts without murmur or dilatation. As Warburg points out, systolic murmur and accentuated P_2 are by no means a rare phenomenon in normal subjects. Of course, the 56

patients of my own series referred to above had had carditis, which is an invariable accompaniment of acute rheumatic fever; only, it has been impossible, at least as regards most of the cases, to establish the diagnosis on the basis of the stated findings. Some of the fifty-six said that they had been told that after a rheumatic fever the heart was in poor condition, and a couple of them had on that account been unable to get life insurance without paying a higher premium. After the result of the after-examination this matter was, however, satisfactorily settled.

Of the 35 patients who at the after-examination were found to have heart disease, 6 had during their hospitalisation presented no signs whatever of cardiac involvement, while in the remaining 29 some affection or other of the heart had been diagnosed already during their stay in the hospital. In the case of 15 of the latter, the diagnosis had however been made on the basis of signs so uncertain that they would hardly to-day be accepted as evidence of heart disease. Of the 21 who at the after-examination presented well developed, sure symptoms of heart disease there were 2 in whom no signs of cardiac involvement had been established at their admission to the hospital. In the case of the 19 others, the diagnosis of heart disease had been made, but only in 11 of them had the signs been sure. It seems to me that this clearly shows the great uncertainty — as also pointed out by Warburg — of a diagnosis of heart disease made during the acute attack. Moreover, all these findings emphasise the importance of not worrying the patients by informing them of cardiac lesions or heart disease on so feeble a basis as we have seen here. But such patients should be followed for some years, and if signs of mitral stenosis or other valvular disease develop they should, of course, be told of the fact, so that they may choose some occupation not demanding too great physical exertion.

Non-rheumatic Heart Disease.

Cardiac affections not of rheumatic origin were found in 8 women. Six of them had hypertension, one thyreotoxicosis, one degeneration of the myocardium (cause unknown).

Chronic, rheumatic Affections of the Joints.

A. Earlier Investigations.

It is a much debated problem whether there is any pathogenetic connexion between rheumatic fever and chronic polyarthritis. That such is the case is maintained specially by German authors. Pribram (1901), for instance, describes the permanent condition which is considered as a condition following acute rheumatic fever as secondary, chronic polyarthritis. Freund (1929) writes that »repeated attacks not infrequently result in lasting articular lesions» and points to the many cases of chronic polyarthritis in a series of ambulant patients with affections of the joints. Anton Fischer (1933) says that in the great majority of cases the inflammation in the joints disappears entirely; only in a few does it become chronic, either after the first attack or after a recurrence.» Of 201 cases of secondary chronic polyarthritis, he found that 65 per cent had developed as direct sequel to rheumatic fever, 35 per cent as sequel to a recurrence. Mueller (1933) thinks that the passage of an acute polyarthritis into the chronic state is by no means uncommon, but that it only occurs in cases that from the beginning have been characterised by a mild progression. Klinge (1930) considers chronic polyarthritis as form of development of the acute attack. Bantin (1935) thinks, from study of 391 patients with diverse rheumatic affections, that persons who have had rheumatic fever are very sensitive to atmospheric changes, — that they have become »erkaeltungs-allergische», — and that the secondary chronic polyarthritis cases are recruited from that category.

Of Scandinavian authors, Kahlmeter, especially, believes in a relationship between the two diseases. In a study of the condition of the hearts of a series of patients with acute or subacute rheumatic fever and with primary or secondary chronic polyarthritis he has shown that there is great difference between the frequency with which cardiac lesions are found in patients with primary chronic polyarthritis and in patients with acute affections of the joints, while the difference in that respect is not nearly as great between patients with secondary chronic polyarthritis and those with acute articular affections. From this, he concludes that there exists a secondary chronic, rheumatic polyarthritis with the same etiology

as acute rheumatic fever, and that the true rheumatic infection is not the cause of primary chronic polyarthritis. Later, Kahlmeter has, however, abandoned the division into secondary and primary forms, because he believes it impossible clinically to distinguish between the two and thinks that there between them and acute polyarthritis are cases that form a labile transition.

Edstrom (1936) found chronic polyarthritis in 21 per cent of his large series of patients with past rheumatic fever. He points out that the liability to chronic affections of the joints increases with the age at first attack of rheumatic fever and with the number of recurrences. He does not mention, though, whether he has seen cases of primary chronic polyarthritis among his patients.

Jansen (1920) found that in the great majority of patients with rheumatic fever the joints were sound when the acute stage was past. In some cases it seemed, however, as if the disease would not come to an end, but terminated in a picture of chronic polyarthritis with its swelling, stiffness and deformation of the joints and contracture and atrophy of the muscles. It will be very difficult to distinguish such a case from one of primary chronic, progredient polyarthritis. Of 133 cases treated by Jansen for »polyarthritis» between 1915 and 1919, one hundred and thirteen belonged to this group.

Ehrstrom (1924) has noticed that many patients after an acute polyarthritis get indefinite pains and a feeling of stiffness in the joints and muscles, but that the objective signs are very slight.

Jespersen (1935) has shown that there is no relationship between rheumatic fever and primary chronic polyarthritis, but he finds that rheumatic fever is not infrequently followed by a characteristic disease in the joints (secondary rheumatic arthritis). Among his patients this was the case in 28.9 per cent of the women and in 19.1 per cent of the men. Besides, there are many who get pains in different joints, but without objective, chronic changes in the latter. Like Edstrom, he find that secondary chronic arthritis is more frequent the older the patient is when he first gets rheumatic fever and the more recurrences he has had. He describes the characteristics of secondary chronic arthritis and points out that the disease oftenest attacks the large articulations, specially the joint-capsule, and that as a rule it is not invalidating.

Many authors, specially among the English and French, but also some German, deny that there is any connexion between rheumatic fever and chronic polyarthritis. Conta (Munich, 1930) examined 204 patients with past rheumatic fever after an average time of eleven and a half years and found that 16 per cent of them had slight rheumatic pains under atmospheric changes, but only two had secondary arthritis. According to Monroe (England, 1939), the «rheumatic» symptoms disappear entirely in most of the cases, and the presence of a lasting articular lesion that should play a rôle in the later development of chronic polyarthritis is merely hypothetical. Gelman (Germany, 1925) considers the problem as still unsolved, but believes himself that there is no relationship between the two diseases. He rejects the conclusion drawn by Klinge from the finding of Aschoff bodies in the myocardium and articular tissue in some cases of chronic arthritis, that both the chronic and the acute forms of that disease should be due to the rheumatic process, and thinks it more reasonable to conclude that the nodules are not of an absolutely specific character. According to Schottmueller (Germany, 1934), continued returns, for many years, of more or less severe pain in the joints are not uncommon in elderly individuals, but fortunately oftenest without the fatal tendency to deformation and ankylosis. Bach (England, 1935) found only 2 cases of chronic polyarthritis among 400 patients with rheumatic heart disease and says that according to his experience the articular manifestations of rheumatic fever invariably subside completely and leave no signs of chronic joint involvement.

Svend Clemmesen (1940) holds the concept of a gradual transition between rheumatic fever and chronic polyarthritis for untenable and thinks that it in the presence of any atypical, subacute or long-lasting rheumatic fever should be closely considered whether the case is not, in fact, one of incipient chronic polyarthritis. The etiology of the two diseases is different, because the sex incidence of rheumatic fever according to all investigations seems to be equal, perhaps with a slight predominance for the males, whereas every considerable material of chronic polyarthritis cases shows about 80 per cent of women to 20 per cent of males (Gram, Heidemann). Clemmesen further believes that in the etiology of the latter disease there is a special female sex factor, while no such can be demonstrated for rheumatic fever. And as a further argument against a

common etiology for the two diseases he points to the fact that whereas the number of rheumatic fever cases in Denmark from 1900 to 1937 went down from 28 to 7 per 10,000, the number of patients with chronic polyarthritis admitted to the hospitals rose from about 500 in 1930 to about 800 in 1937 (these figures are for hospitals outside Copenhagen, but the figures for the Copenhagen hospitals are about the same).

Also Moltke (1933) thinks that the rôle of the rheumatic infection in the etiology of chronic polyarthritis has been considerably exaggerated, and according to Warburg (1931) the simultaneous presence of mitral stenosis and contracture of the joints is very rare.

The presence of subcutaneous nodules both in patients with rheumatic fever and with chronic polyarthritis is held by many authors (Klinge, Dawson, Clawson and Wetherby, Poynton and Schlesinger) to be the conclusive proof of the common etiology, because they consider these nodules as identical in the two diseases. Dawson regards them as representing in each of them a different phase of the same fundamental, pathologic process. This view is shared by Clawson and Wetherby, who find the nodules in both diseases identical both macroscopically and microscopically. Poynton and Schlesinger write that »probably the most convincing evidence of a direct relationship between rheumatic fever and rheumatoid arthritis is the discovery in both of subcutaneous nodules.»

Other authors (Keil, Collins) think, however, that both the clinical and the pathoanatomical difference between the nodules in the two diseases is more striking than the similarity; and in his monograph on rheumatic fever, Vaubel (1938) takes exception to the great »worship» of nodules and points out that their identity in the two diseases has not yet been proved. For the present it must be realised that subcutaneous nodules may develop both in rheumatic fever and in certain forms of arthritis, — and even without any other manifestation whatsoever. But though it is true that there are certain points of similarity between these formations, this does not justify the identification of any disease in which they occur with rheumatic fever.

These subcutaneous nodules, which play so great a rôle specially in the English and American literature, are a very rare phenomenon in Denmark, at least in rheumatic fever, while in chronic polyarthritis they are considerably more frequent. Of 215 patients

in my material, only one had had them, according to the case record. It is possible, of course, that in other cases they may not have been noticed, which may easily happen if they are not specially looked for; but in the last couple of years I have among between forty and fifty patients with rheumatic fever seen only one with nodules, though I have searched particularly for them. In English and American materials they are variously stated to occur in from 10 to 25 and 50 per cent of cases and their occurrence invariably associated with severe cardiac involvement and a sign of bad prognosis. Perhaps their seldomness in Denmark is due to the fact that chronic heart diseases, as my material shows, are relatively infrequent there. All the more should it perhaps be noted that they were described already in 1880 by a Danish author, Hirschsprung, who in that year published 3 cases of rheumatic fever with nodules. The microscopy, which was made by Bernhard Bang, is the first good description given of these formations.

B. Own Results.

Among the 209 patients examined, I did not find a single one with primary, progressive polyarthritis, nor did I find any one with sure secondary rheumatic arthritis such as described by Jespersen. My most frequent finding (in 39 patients) was complaints of periodical pains in the joints without either subjective or objective, attendant changes in the latter or their surroundings, and without any other restriction of mobility except that movement was painful. As a rule, the pains were brought on by outside circumstances, oftenest by »cold or damp weather»; sometimes they came when the patient »got a cold», or sore throat, or »influenza».

A considerably smaller group (10 patients) told of changes in the joints, nearly always in the form of swelling of their surroundings. I did not myself see any cases of such changes, except a very few of osteoarthritis of the knee joints, of which it must be supposed that they had no etiologic association with the rheumatic fever.

From Table VI it will be seen that very few of the patients in my material had affections of the joints when examined, and that most of those with whom it was the case were women. Also in my material the tendency to get such affections was greater the older the patient had been at the time of the first attack of rheumatic fever; the

Table VI.

Incidence of articular Lesions in the Series of 209 examined Patients.

	Female	Male
Total examined.....	121	88
Periodical pains in the joints, but no articular changes	29	10
» » » » » and subjective changes	9	1
Total	38	11
do. (per cent)	31.5	12.5
do. female + male	49 (= 23.5 per cent)	

average age at first attack for all those with articular lesions being about 20 years, for those with heart disease only about 12 years. On the other hand, the incidence of recurrences would appear to be higher for those with heart disease, the averages being respectively 1.3 and 1.8 for the two groups.

Rheumatic heart disease is an infrequent occurrence in chronic rheumatic arthritis. I found this combination only in 3 patients, two of whom had only been »observed for rheumatic heart disease», while the third had an aortic lesion.

The result of my investigations is thus that there is no relationship between rheumatic fever and chronic polyarthritis, but that there in some cases, mostly in women, is a periodical occurrence of pain in the joints, oftenest evoked by cold and as a rule not accompanied by articular changes.

Discussion and Conclusions.

A. *The Tendency to Recurrences.*

As regards the tendency to recurrences, my material shows good accordance with those of other investigators both as regards the number of recurrences, the time of their occurrence and the intervals between the initial attack and the different manifestations. In Chart IV it is seen how Edstrom's curves and my own are nearly identical.

B Rheumatic cardiac lesions.

The most striking result of my investigation concerning the frequency of heart disease after proved rheumatic fever is the small number of such cases found, viz. 16 per cent after an observation period of ten to twenty years. The figure is even the maximal one, inasmuch as it includes the two groups labelled respectively »observed for rheumatic heart disease» and »possibly rheumatic heart disease»; in other words the patients in whom there were no absolutely sure signs of cardiac involvement. The small number of cases does not permit me to form conclusions respecting the incidence of the various types of the disease; I must therefore confine myself to considering the group as a whole. Still, it can be seen that the frequency distribution of the different types agrees well with the showing of other, larger materials. Also according to my findings, mitral stenosis is the most frequent form of valvular lesion, and the incidence of this particular valve disease immensely greater in females than in males.

Edstrom found »persisting organic heart disease» in 60 per cent of his patients, which is nearly four times as many as in my material. It cannot be seen, though, on what criteria he has based his diagnosis. In between one-third and one-half of of all his cases with »persisting organic heart disease» the diagnosis was mitral insufficiency; if we deduct these, the 60 per cent become reduced to 35 per cent, but still this is more than twice as many as in my series. It is difficult to find any explanation for this, especially because it, as just said, is impossible to see on what basis Edstrom made his diagnosis of »persisting organic heart disease.»

A specially interesting result was come to by Bland and Jones with a group of 314 children in whom there was no evidence of heart disease following the initial attack of rheumatic fever. After an observation time of ten years they found permanent lesion of the heart in one-fourth of them; in other words the same percentage as I found among 100 young persons in my series (see Table V). I feel particularly justified in comparing my findings with those of Bland and Jones because sure cases of heart disease after recovery from a first attack are extremely rare also in my material.

Boone and Levine followed a group of 225 children who had had no signs of heart disease after the initial rheumatic attack

over an average period of 9.6 years and found after that lapse of time permanent valve lesion in 15 per cent of them, — a smaller percentage than found either by Bland and Jones or by myself.

Most of the analyses published show higher percentages of carditis than mine, also in young persons. Thus, Coombs found of a group of children who had not presented signs of heart disease following the first attack only about 50 per cent completely cured, while my material shows 75 per cent cured out of a group of which a few had signs of cardiac involvement from the start. It is especially with regard to the mortality, however, that the difference is great. Of Coombs's child group, 6 per cent of those with doubtful, and 20 per cent of those with sure heart symptoms from the beginning, died within ten years after the initial attack. Of 100 children in my material, only 7 in all died, and of these only 2 within five years, the others after an average of thirty-three years. A similar bad prognosis as Coombs's is shown by the analyses of Bertram and Black. On the whole it would seem that the heart lesions are severer in the anglo-saxon countries, where rheumatic fever is also considerably more frequent than in Denmark. That serious cases of carditis in connexion with the primary attack are not seen so often there is probably because severe attacks of rheumatic fever are rather uncommon. This is perhaps also the reason why subcutaneous nodules are so rare in Danish cases; nodules being, according to all statements, found especially in the cases that have a very bad prognosis.

Of the type of aortic lesion which Clawson, Bell and Hartzell call «calcified nodular aortic valve deformity» I have not found any case in the clinical material. The postmortem records, on the other hand, showed a number of such cases, but only in a few of them was there any sure evidence of the rheumatic etiology. It is possible that a few cases of this type may have escaped my attention, though. As already said, this lesion occurs chiefly in patients above the age of fifty, and at the time of my examination only 23 were above that age, most of the others were between twenty-five and forty-five. I hardly think, however, that there is any risk of this circumstance making the prognosis appear unduly favorable. This type of aortic lesion is rather uncommon; therefore it will not essentially affect the result as a whole, even if a couple of

the patients in my series should later develop this special form of stenosis.

My study seems to show that in Denmark permanent lesion of the heart consequent on rheumatic infection is rarer than one would expect from the literature. This applies especially to the series as a whole. As regards the children alone, my results accord better with those registered elsewhere; that is to say that the frequency of permanent cardiac involvement is about three times greater for children than for adults. It must be pointed out here that the present study is based exclusively on the polyarthritic manifestation of rheumatic fever.

C. Chronic Polyarthritis.

Jespersen has convincingly shown that there is no relationship between rheumatic fever and primary chronic, progressive polyarthritis. On the other hand, he believes that rheumatic fever is not infrequently followed by a characteristic chronic affection of the joints, secondary chronic arthritis. His material and mine have much in common, being both from hospital services and both from about the same period (his, 1923—24; mine, 1921—30). It seems, though, that his patients were a little older than mine when they got their first attack; at least they were older at the time of their admission to hospital. Thus, only 27.6 per cent of his women were under twenty years old when hospitalised, whereas 38 per cent of mine were under that age, and of the men respectively 37 and 62 per cent in the two materials. Apart from this, these two materials should be excellent objects for comparison, all the more because they are from the same country. And yet there is the striking difference between them that Jespersen found secondary rheumatic arthritis in 28.9 per cent of his women and in 19 per cent of his men, while I did not find a single case of that disease among my patients. It might possibly be because my patients were younger when they had their first attack, and at the time of the after-examination no yet old enough to have got secondary arthritis; but this explanation can hardly be the right one, seeing that I did not find a single case of that disease among them all. If the age were a factor, I must have found at least a few.

Jespersen found complaints of articular pains or of periodical swelling of the joints in 23.6 per cent of the women and in 16.9 per cent of the men. My figures are not much different, respectively 31.5 and 12.5 per cent.

As already said, many other authors believe that rheumatic fever and chronic polyarthritis are related diseases; some because the chronic articular lesions come as sequel to acute rheumatic fever, others on account of histopathologic points of similarity and the occurrence of nodules in both. As Clemmesen points out, it is necessary, however, closely to consider whether an atypically protracted rheumatic fever is not in fact the beginning of a chronic polyarthritis. It is no doubt often such cases that have been called secondary polyarthritis.

As regards the nodules as the missing link in the chain of proof, these formations occur, at least in Denmark, almost exclusively in connexion with chronic polyarthritis and are extremely rare in rheumatic fever. Their value as evidence, therefore, seems to me to be very slight.

Moreover, several authors point to the fact that whereas rheumatic fever occurs with equal frequency in both sexes, chronic polyarthritis is preeminently a female disease (80 per cent, according to Gram and Heidemann). Finally, all authors agree that rheumatic fever often gives rise to valve lesions, while several clinicians, Bach and Warburg among others, have never seen chronic polyarthritis in patients with rheumatic heart disease.

From study of the literature and from the result of my own investigation I feel justified in believing that rheumatic fever does not produce primary chronic, progressive or any other form of chronic polyarthritis, but that patients who have had rheumatic fever are sometimes inclined to get pains in the joints, especially under the influence of cold.

Summary.

With a view to the elucidation of the prognosis in rheumatic fever, the author has followed up and examined 209 patients treated for that disease during the years 1921—30. The material comprises individuals of all ages and of both sexes. The distribution by sex and age groups is shown in Table I and Charts I, II and III. It is

seen from these that the largest number of first attacks falls in the age group 11—15 years, and that there in the age group 21—30 is a great preponderance of females. The causes of this are briefly discussed.

The Tendency to Recurrence.

A. Earlier Investigations

The literature is reviewed for data concerning the frequency of recurrences and the time of their occurrence in relation to the initial attack. It is shown that the findings of the various authors in this respect are more or less similar. Thus, they all agree that the susceptibility to recurrence is greatest in early youth and becomes less with increasing age, and that the recurrences oftenest occur within a few years after the first episode.

B. Own Results.

Half of the cases in the material had had at least one recurrence. Most of these occurred in the first years after the initial attack, but in not a few instances there was an interval of from 10 to 20 years before the first return of the symptoms. The frequency of recurrences in the different age groups is shown in Table II, from which it is seen that the tendency in this respect decreases in inverse ratio to the age at first attack. In Table III is shown the relation, in time, between the occurrence of the recurrences and the initial attack. Finally, the author gives it as his conclusion that although most of the recurrences, by far, occur with ten years after the primary episode, there is no certainty that a rheumatic fever may not recur at any, more distant time.

The Frequency of rheumatic Heart Disease.

A. Earlier Investigations.

The author reviews the literature for data respecting the frequency of chronic rheumatic heart diseases consequent on rheumatic fever such as they appear from the various published materials.

It is shown that it often takes several years for mitral stenosis to develop. There is more or less unanimity as regards the incidence of the various forms of cardiac affection and no great difference of opinion as regards the prognosis for the different types. Aortic stenosis is the only lesion which persists for any considerable time. Finally, the affection is described which Clawson, Bell and Hartzell call »calcified nodular aortic valve deformity.»

B. Own Results.

At the end of the observation period 16.7 per cent of the 209 patients had chronic rheumatic heart disease or had died from such. Table IV shows the different types of lesion found; a few of them are discussed in some detail. There was no aortic lesion among them of the »calcified nodular valve deformity» type. Among 4,000 post-mortem records from the period 1924—41, twenty-four cases were found which might be considered as belonging to this type, but only in connexion with 4 of them was there any mention of previous rheumatic fever. In Table V the material is divided into two groups according to whether the patients had had their first attack before or after the fifteenth year of life. As the Table shows, there were about 3 times as many with rheumatic heart disease in the younger of these groups than in the older. Of all the 209 patients followed, only 3 (1.4 per cent) died within 5 years and only 4 (1.9 per cent) within ten years after the first attack.

The Diagnosis of cardiac Affections during the acute Attack.

In 56 of the patients whose hearts were found in a sound condition when they were after-examined, rheumatic cardiac disease had been diagnosed during their stay in the hospital. The methods by which the diagnosis was established is described. Thirty-six of them were at the after-examination examined stethoscopically and no signs of cardiac affection found; and in the case of 11 of these this examination was further supplemented by roentgen

examination and electrocardiography, all with negative result. Similar findings are known also from the literature. It is pointed out that systolic murmurs and accentuated P_2 are not uncommon phenomena in normal subjects, either. For the sake of comparison, the conditions found in the cases where the after-examination revealed affections of the heart are described. Only in about half of the cases in which indubitable cardiac affection later developed had it during the initial attack been possible to diagnose heart disease.

Chronic rheumatic Affections of the Joints.

A. Earlier Investigations.

A review is given, first of the works of those authors who maintain that there is a relationship between rheumatic fever and chronic polyarthritis, next of a number of works whose authors take the opposite view. It is mentioned that the presence of subcutaneous nodules both in patients with rheumatic fever and in patients with chronic polyarthritis is considered by some as the conclusive proof of a common etiology for the two diseases, while by others this is not considered as proof. It is noted that in Denmark nodules are rare in rheumatic fever, in contrast to what is the case especially in anglo-saxon countries.

B. Own Results.

No case was found either of primary chronic, progressive polyarthritis or of the secondary rheumatic arthritis described by Jespersen. The most frequent finding was complaints of periodical pains in the joints, without swelling of the latter. Such pains were complained of by 39 patients, while periodical changes in the joints were found only in 10 cases. The results of the observations are represented in Table VI, which shows that women, especially, are susceptible to such articular pains. Affection of the joints in connexion with chronic rheumatic carditis was rare, being found only in 3 cases of 49.

Discussion and Conclusion.

A. *The Tendency to Recurrence*

The author's findings respecting tendency to recurrences agree well with those of other investigators, both as regards the number and time of the recurrences and the interval between the first attack and the return of the symptoms.

B. *Rheumatic Heart Disease.*

The author notes as characteristic the small number of the patients in his material (16 per cent) in whom rheumatic heart diseases were found. He gives this as the reason why he has not ventured to form any conclusions with regard to the incidence of the different types of cardiac affection. He compares his results with those of various other authors and shows that their findings for the greater part reflect a more serious condition than his own, especially as regards the fatal nature of the disease. The connexion between the presence of subcutaneous nodules and severe cases of carditis is spoken of. Among his cases there were none of the calcified type of aortic stenosis described by Clawson, Bell and Hartzell. Finally, he concludes that in Denmark permanent injury to the heart consequent on rheumatic fever is rarer than one would expect from findings elsewhere. Only as far as children are concerned do his observations seem to agree better with those of other authors; the frequency of cardiac involvement being in his material 3 times greater for children than for adults.

C. *Chronic Polyarthritis.*

The author discusses his own findings and compares them especially with those of Jespersen, because the material of that other Danish investigator should be particularly suitable for comparison with his own. He therefore also notes it as all the more striking that Jespersen found quite a number of patients with secondary rheumatic arthritis, whereas there was not a single case of that character among his own. He discusses whether the cause of this should be the circumstance that his own patients were younger at

the time when they had their first attack and therefore at the time of the after-examination not old enough to have gotten secondary arthritis. As regards the occurrence of periodical pains in the joints and tumefaction of the latter, he finds that there is good agreement between the two materials. He rejects the idea of the subcutaneous nodules as conclusive evidence of a relationship between rheumatic fever and chronic polyarthritis. Finally, he concludes that rheumatic fever does not give rise to primary chronic, progressive polyarthritis or other forms of that disease, but that patients who have had rheumatic fever are inclined to get periodical pains in the joints, especially under the influence of cold.

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Concurrent development and subsequent dissociation of anaphylaxis, allergy and immunity in tuberculosis.

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In a previous article (1941) we stressed the confused state of our knowledge concerning the anaphylactic, allergic and immune manifestations in tuberculosis, which various factions believe to be similar or different biological phenomena. After having reviewed literature and placing these biological reactions in juxtaposition, we presented a number of experimental data which aimed to demonstrate that tuberculo-protein as such fails to immunize against virulent tuberculous infection, but sensitizes guinea pigs both actively and passively to fatal anaphylactic shock, without conferring allergic hypersensitiveness on the animals. Antianaphylaxis could readily be induced in tuberculous animals, which were both tuberculo-protein anaphylactic and tuberculin allergic, without the state of allergic hypersensitiveness being abolished. Finally, the state of allergic hypersensitiveness could be completely removed from tuberculo-immunized guinea pigs without any loss of acquired immunity. From these experiments we concluded that the specific antibodies responsible for tuberculo-anaphylaxis and tuberculo-immunity are non-identical and that the state of tuberculo-allergy does

not at all depend upon specific antibodies. Thus it would appear that the tuberculo-biological phenomena of anaphylaxis, allergy and immunity are independent and separable and that their concomitant presence in subacute and chronic tuberculosis is merely fortuitous. But to produce concurrently all these three biological states in one and the same animal and subsequently to separate them individually is not known to us to have been accomplished in tuberculosis. The burden of this report is just such an attempt. We are inclined to believe that such an experiment will have definite connotation for our understanding of immunity in experimental and clinical tuberculosis. Such implication is in point the recent observations of the immediate defense skin reaction at the site of BCG-revaccination in previously vaccinated but persistently tuberculin negative persons (Birkhaug, 1941; Thorkildsen, 1942). This appears to be the clinical manifestation of the experimental state of tuberculo-immunity without allergic hypersensitiveness which we have called *iathergic immunity*.

Materials and methods.

Animals. — Thirty-six normal and tuberculin negative guinea pigs were divided into 3 equal groups hereafter called (I) iathergic-immune, (II) allergic-immune, and (III) controls. Group I weighed 549 sigma 55.15 g before the experiment began; group II weighed 520 sigma 86.26 g, and group III weighed 607 sigma 82.17 g. Animals of the same sex were placed in groups of 6 in metal cages ($46 \times 46 \times 35$ cm) having closed sides and topped with a metal wirelid having 3 cm^2 wide meshes. The diet consisted of approximately 50 g turnips, 75 g hay, 10 g oats and 25 g fresh brown bread. No extra water was given. The diet was supplemented thrice weekly with cod-liver oil and «Vitakalk» (a calcium-phosphorus, vitamin D, etc. preparation which greatly increases the complement and reduces intercurrent infections during the autumn-winter season). The temperature of the animal house varied between $15\text{--}18^\circ \text{C}$. During the experimental period no intercurrent infection occurred in the animal house.

Anaphylactic sensitization. — The animals in groups I and II were injected intravenously in the exposed jugular vein with 1.92 mg BCG tuberculoprotein contained in 2 cm^3 of saline, adjusted

with ammonia to pH 7.2. The solution was clear. The punctured vein was not ligatured but was held compressed with contiguous tissue until bleeding ceased. This precaution was followed in order to have accessible veins for the assaulting shock dose of the specific anaphylactogen. Group III was not sensitized anaphylactically.

Tuberculo-immunization. — The day following the tuberculo-protein anaphylactic sensitization, the animals in groups I and II were injected in the left thigh muscles with 1 cm³ molten paraffin (Parawax 54° C M. P.) containing 200 mg semi-dried BCG from a 4 weeks' old Sauton's culture. The syringe and needle were heated to about 60° C and the evenly partitioned BCG-paraffin mass was rapidly aspirated into the syringe and immediately injected into the left thigh muscles. After the withdrawal of the needle, a finger pressed on the punctured site to prevent escape of the BCG-paraffin mass before it hardened *in situ*. The inconvenience to the animal of having 1 cm³ of molten (56—57° C) paraffin injected intramuscularly seemed negligible.

In order to ascertain whether or not the BCG submitted to this momentary temperature were still alive, we mixed equal amounts of BCG and saline heated to 56—58° C for 10 minutes and inoculated Löwenstein solid egg media with the material. Approximately two-thirds of the BCG proved to be alive after the ordeal. The immunizing focus should therefore contain a mixture of living and dead paraffincoated BCG.

When the experiment was terminated approximately 130 days after the injection with the BCG-paraffin mass and 50 days after the inoculation with the virulent test dose of human tubercle bacilli, we found that 8 out of 12 group I (iathergic-immune) animals, or 66.7 percent, had retained the BCG-paraffin focus intact. Only 4 out of 12 group II (allergic-immune) animals, or 33.3 percent, had done likewise. We have previously (1940) described the greater tolerance of the BCG-paraffin mass in the desensitized iathergic-immune animals. Doubtlessly, an intimate association exists between the permanent retention of the primary focus and the complete or nearly complete tuberculo-resistance in the iathergic-immune animals. It will be recalled that Lurie (1933) has shown that in the presence of sufficient residual primary lesions, the bacilli of reinfection are quickly destroyed without preliminary multiplication.

Desensitization with tuberculin. — Group I iathergic-immune animals were submitted to a regimen of persistent allergic desensitization with tuberculin in order to prevent the development of tuberculo-allergy during the entire experiment. The course of desensitization began the day after the intramuscular injection with the BCG-paraffin mass and was repeated every Monday, Wednesday and Friday. The desensitizing dose consisted of 100 mg undiluted tuberculin, prepared by the State Veterinary Institute at Oslo. The injections were made subcutaneously along the legs and abdomen at constantly shifting sites. In order to ascertain if desensitization was accomplished with the thrice weekly injections of 100 mg tuberculin, we made weekly intracutaneous tests with 10 mg tuberculin, with readings both after 24 and 48 hours. Tables 1 and 2 present the results of these intracutaneous tests. Three refractory guinea pigs (25 percent) showed incomplete desensitization 6 weeks after the start of the experiment. The reactions were minimal, but nevertheless necessitated that the desensitizing dose was increased to 200 mg tuberculin thrice weekly. This dose was thenceforth retained until the experiment was terminated without the course of desensitization having unduly compromised the general health of the animals. We have previously (1940) accounted for the excessive tuberculous pneumonia which some authors found always to supervene on the excessive use of tuberculin in tuberculous guinea pigs. In order to prevent such accidents, we have purposely made use of the smallest possible doses of tuberculin for desensitization purpose, with the result that we rarely observe croupous tuberculous pneumonia in our iathergic-immune animals. The criticism that small doses of tuberculin cannot fully desensitize tuberculo-infected guinea pigs is refuted by our crucial test of injecting fatal doses of tuberculo-protein intravenously in our iathergic-immune animals with impunity, as will be demonstrated later in this present article.

Tables 1 and 2 clearly show that while the allergic-immune animals in group II present an increasing allergic hypersensitiveness in 100 percent three weeks before the test inoculation with virulent human tubercle bacilli, the iathergic-immune animals in group I show complete tuberculin desensitization in 75 percent and a relatively insignificant cutaneous allergy in the remaining 25 percent. In fact, the difference in volumetric erythema and infiltration between these two groups is approximately 16 times greater than

their standard deviations when reading was made after 24 hours ($t = 15.680$ and $P \leq 0.001$) and 7 times greater after 48 hours. To those recalcitrant believers in the immunizing virtue of allergic hypersensitiveness who attach importance to that insignificant degree of cutaneous allergy which is present in 25 percent of our *iathergic-immune* animals, we should like to restate »that if allergy is synonymous with immunity, then we should expect the hyper-allergic animals to present the completest form of tuberculo-immunity, which decidedly is not the case.»

Virulent superinfection. — Exactly two months after the subcutaneous injection of 200 mg BCG in 1 cm³ molten paraffin in the *iathergic-immune* group I and the allergic-immune group II animals, we found it appropriate to submit all the three groups of animals to a virulent tuberculous infection. A dose of 0.005 mg moist weight of a human strain of tubercle bacillus (»Tuxen») was injected *intraperitoneally* into each of the 36 animals. The Löwenstein culture of the »Tuxen» strain was 4 weeks old. By serial dilutions in saline, seeded out on large tubes of Löwenstein's solid egg medium, we found that the infecting dose contained approximately 37,167 viable bacilli (colonies). It should be remembered that the test dose was administered *intraperitoneally* inasmuch as this route provokes a more rapidly disseminating tuberculosis than by the subcutaneous route. Thus the *intraperitoneal* test infection presents a greater tax on the animal's tuberculo-resistance than does the subcutaneous route.

Post-infection tuberculin reactions. — In order to ascertain the status of the organism's response to tuberculin (allergic hypersensitiveness), repeated intracutaneous tests were made with 10 mg tuberculin in all the 36 animals during the third and seventh postinfection weeks while the *iathergic-immune* group was also tested during the second and fifth post-infection weeks. Tables 1 and 2 show that respectively 2 or 3 animals in the *iathergic-immune* group (17—25 percent) resisted complete tuberculin desensitization and presented a relatively insignificant volume of erythema and induration and a still more insignificant area of central necrosis during the entire post-infection period. These same recalcitrant animals showed a marked tendency to produce fluctuating abscesses at the sites injected with 200 mg tuberculin. The contents of these abscesses consisted of a conglomeration of adventitious bacteria

Chart 1

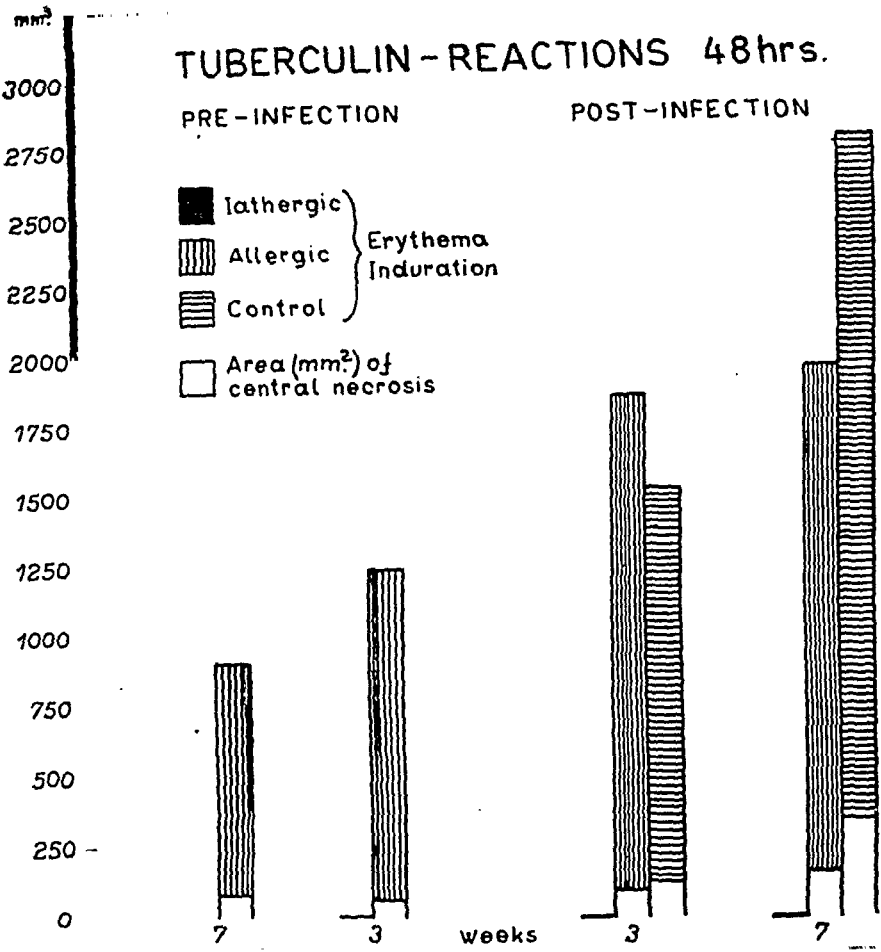


Chart 1. Tuberculin Reactions 48 hours after the Intracutaneous Injection of 10 mg Tuberculin.

with no acid-fast bacilli. After incision prompt healing took place. The capacity to resist complete desensitization resulted also in a tendency to a more hyperplastic tuberculosis (vide Tables 3—4, nos. 845, 847 and 868) than in the completely desensitized iatrogenic-immune animals.

The allergic-immune and control groups of animals, on the other hand, presented regularly (100 percent) hyper-allergy, with excessive central necrosis during the post-infection period. A perusal of the statistical data in Tables 1 and 2 leaves little room for doubt that desensitization was complete or nearly complete in the iatrogenic-immune animals. Thus we observe that the difference in volu-

Table 2.

Pre-infection and post-infection tuberculin reactions.

Statistical analysis of area (in mm²) of central necrosis after intracutaneous injection of 10 mg tuberculin.

A. Reading in 24 hours.

Weeks before/ after virulent infection	I. Lathergic-immune				II. Allergic-immune				III. Allergic-control				Probability			
	Posi- tive				Posi- tive				Posi- tive				I VS II			
	Central Necrosis				Central Necrosis				Central Necrosis				I VS III			
	Area	Sigma	%		Area	Sigma	%		Area	Sigma	%		t	P	t	P
Before																
8	0	0	0		0	0	0		0	0	0		—	—	—	—
7	0	0	0		91	102.1	75		—	—	—		—	—	—	—
6	0	0	0		—	—	—		—	—	—		—	—	—	—
5	0	0	0		—	49.4	—		—	—	—		—	—	—	—
3	25	3.6	7.3		53	—	100		—	—	—		—	—	—	—
1	0	0	0		—	—	—		—	—	—		—	—	—	—
After																
2	0	0	0		—	—	—		—	—	—		—	—	—	—
3	17	0.5	0.9		89	87.0	100		66	30.0	100		7.252	< 0.001	3.229	< 0.01
5	17	1.0	1.3		—	—	—		—	—	—		—	—	—	—
7	17	2.0	4.7		125	80.2	100		300	131.6	100		7.507	< 0.001	5.079	< 0.001

B. Reading in 48 hours

B. Reading in 48 hours															
Before															
8	0	0	0	0	0	0	0	0	0	—	—	—	—	—	—
7	0	0	0	0	0	86	83.5	—	—	—	—	—	—	—	—
6	0	0	0	0	—	—	—	—	—	—	—	—	—	—	—
5	0	0	0	0	—	—	—	—	—	—	—	—	—	—	—
3	25	4.3	7.6	100	76	56.9	—	—	—	—	—	—	—	—	—
1	17	3.3	7.6	—	—	—	—	—	—	—	—	—	—	—	—
After															
2	0	0	0	—	—	—	—	—	—	—	—	—	—	—	—
3	8	0.2	0.8	100	107	75.6	100	125	42.4	3.087	< 0.01	4.184	< 0.001	0.688	0.50
5	17	1.3	2.9	—	—	—	—	—	—	—	—	—	—	—	—
7	17	2.4	2.0	100	159	80.9	100	362	140.6	8.482	< 0.001	6.319	< 0.001	4.150	< 0.001

metric erythema and induration between the iathergic-immune and allergic-immune or the control groups was 9 to 13 times greater than their standard deviations, all these differences being of absolute statistical significance. Likewise, the differences in central necrosis between the iathergic-immune group on the one hand and the allergic-immune or control groups on the other hand, were from 3 to 8 times greater than their standard deviations and always of absolute statistical significance. It must be admitted, therefore, that our claim of complete or nearly complete tuberculin anergy in the iathergic-immune animals is made good.

Post-infection weight. — We have already stated that before the experiment began the iathergic-immune group I animals weighed 549 sigma 55.15 g, the allergic-immune group 520 sigma 86.26 g, and the control group III animals weighed 607 sigma 82.17 g. When the experiment was terminated four months later we found that group I weighed 513 sigma 69.87 g, group II weighed 451 sigma 100.54 g, and group III weighed 433 sigma 30.17 g. This proves that the iathergic-immune animals, in spite of the extra impositions of the thrice weekly injections with 100—200 mg tuberculin plus the intraperitoneal inoculation with 0.005 mg human tubercle bacilli, had held their weight nearly undisturbed during the entire experiment with a total loss of 37 g, or $1/15$ th of the original body weight. The allergic-immune animals, on the other hand, had lost about 70 g, or $1/7$ th of the original body weight, while the control animals had lost 174 g, or $1/3$ d of the original body weight. These differences in loss of body weight is proportional with the everity of the tuberculous infection in the three respective groups of animals, as will be demonstrated later. Statistical evaluation revealed that the difference in final body weight between group I and group III was of slight but unreliable significance ($t = 2.247$ and $P = 0.03$) while the difference between groups II and III fell far short of any significance ($t = 0.434$ and $P = 0.65$). Interpretation of these statistical symbols is given under »Quantitative measures of degree of tuberculosis» later in this article.

Mortality rate. — Two control group III animals died spontaneously of +++ and ++++ generalized tuberculosis (vide C 838 and C 844) respectively 50 and 54 days after the virulent superinfection.

Because these two animals gave proof of a sufficiently advanced hyperplastic tuberculosis which could be assessed quantitatively, we decided to terminate the experiment for the purpose of demonstrating and separating the concurrent states of tuberculo-anaphylaxis, tuberculo-allergy and tuberculo-immunity, the very purpose of these experiments.

The animals were sacrificed between the 55th and 65th post-infection days in the following manner: in the iathergic-immune group I, six animals died in acute anaphylactic shock (bronchospastic asphyxia) while the remaining six animals survived the production of antianaphylaxis without succumbing with allergic intoxication and were subsequently killed. In the allergic-immune group II, six animals died in acute anaphylactic shock while the remaining six animals survived the production of antianaphylaxis but died subsequently with allergic intoxication. The surviving 10 control group III animals, which had not been sensitized anaphylactically, died in allergic intoxication.

Dissociation of anaphylaxis, allergy and immunity in tuberculosis.

Tuberculo-anaphylaxis in iathergic-immune animals. — The crucial point in these experiments is the concurrent development in one and the same animal organism of tuberculo-anaphylaxis, tuberculo-allergy and tuberculo-immunity and subsequently to demonstrate and dissociate the two former states, leaving behind the effects of the immune state. It will be recalled that the first part of this experiment, namely the separation of tuberculo-anaphylaxis and tuberculo-allergy was successfully carried out in our last publication (1941) and that the separation of tuberculo-allergy and tuberculo-immunity had likewise been done in several stages during 1937—1940. The present series of experiments is a combination of the aforementioned investigations.

Table 3 presents the quantitative data on the production of anaphylactic shock in six of the tuberculoprotein sensitized, BCG immunized, tuberculin desensitized and virulently infected iathergic-immune animals. The specific BCG-tuberculo-protein shock dose was administered intravenously in doses varying from 0.96 to 4.80 mg crystalline tuberculoprotein suspended in neutral

saline solution (pH 7.2). The assaulting dose produced the classical symptoms of acute anaphylactic shock, with chills, scratching of the nose, bristling hair, spasmodic sneezes, violent jumps, tonic and clonic convulsions, prostration, slowing down of respiration, mouth opening with each violent inspiratory effort, fall in temperature (as low as 28° C), discharge of urine and feces, and breathing ceasing 4 to 7 minutes after the injection of the specific anaphylactogen. Autopsy revealed continued heart beats and supervening heart-block with 2—3 auricular beats to one ventricular beat. We re-confirmed our previous observation (1941) that active peristalsis occurred post-mortem in the entire length of the gastro-intestinal tract inclusive the stomach, contrary to the report by Auer and Lewis (1910) of »no definite peristalsis of colon, caecum or stomach.» The gastro-intestinal tract, uterus, lungs and diaphragm showed occasionally congestion and ecchymotic flecks. The rigid distention of the lungs was the most conspicuous feature. Although the weight of the lungs was not notably increased, we found that their volume was doubled or nearly doubled. While the normal ratio between the weight and volume of guinea pig lungs is approximately 1: 1.2, a glance at Table 3 shows that it was increased on the average to 1: 2.33 in these anaphylactic animals. Sections of the lungs revealed an extreme dilatation of the alveoli, with numerous interstitial and intraalveolar hemorrhages, not due to simple emphysema, but to a violent contraction of the bronchioles and rupture of their smooth muscle fibers. It will be recalled that the bronchioles in the guinea pig lungs are excessively supplied with smooth muscle fibers. The violent spasms of the bronchioles caused retention of the inspired air within the dilated and ruptured alveoli. Thus death was brought about by bronchospastic asphyxia rather than by circulatory failure.

The next important observation in these six guinea pigs was the high degree of tuberculo-resistance against the virulent test infection with human tubercle bacilli. Abscesses were entirely lacking in the abdominal muscles penetrated by the needle through which the virulent inoculum was injected intraperitoneally. Hyperplasia in the omental and mesenteric lymph nodes, which always results from intraperitoneal infection with virulent tubercle bacilli, was completely absent, the spleen and liver were nearly normal in size and appearance, and the lungs showed occasionally a few discrete

gray tubercles which were not caseated. The general lymph nodes presented likewise a remarkable normal appearance and volume. Two animals presented no macroscopic lesions whatsoever (D 861 and 867). We shall return later to the quantitative evaluation of the visceral data.

Antianaphylaxis and anergy in iathergic-immune animals. — Having established in the preceding experiment that an excessive state of tuberculo-anaphylaxis was present in the iathergic-immune group I animals, we planned to produce antianaphylaxis in the remaining six animals in this group. The jugular vein was exposed and the needle fixed *in situ* with a ligature. The specific BCG tuberculo-protein, dissolved in neutral saline (pH 7.2), was then injected into 3 animals (D 847—849) in exceedingly small doses of 0.096 mg every minute during 10 minutes until a total of 0.96 mg tuberculoprotein had been injected. A transient and moderately severe anaphylactic shock was invariably produced following the first injection, but the attack passed off rapidly until no reaction was provoked after the third or fourth interspersed injections. In the 3 remaining animals an extra dose of 2.88 or 4.80 mg tuberculoprotein was added to the 0.096×10 mg doses injected during the previous 10 minutes. We have earlier (1941) described the high tuberculin activity of the natural or purified BCG-tuberculoprotein which we employ in these experiments. Although it fails to sensitize normal guinea pigs allergically towards tuberculin, the BCG-tuberculoprotein kills tuberculous guinea pigs regularly in 2 to 14 hours after the intravenous injection with 1 to 3 mg tuberculoprotein. Our purpose in injecting the extra amount of tuberculoprotein on top of the anaphylactic desensitizing dose, was to prove that our iathergic-immune animals were truly allergically desensitized viscerally as well as cutaneously and hence should not succumb in allergic intoxication. A glance at Tables 1 and 2 will show that these animals were completely or nearly completely cutaneously anergic toward tuberculin. Our supposition was confirmed. Every one of these 6 animals survived the ordeal of being converted from the anaphylactic to an antianaphylactic state without presenting any symptoms or signs of allergic intoxication during the following 16—24 hours when they were killed for histopathological purpose. Autopsy revealed no exudations nor hemorrhages which always

attend tuberculin intoxication, but only the same proofs of complete or nearly complete tuberculo-resistance which we have described above in the other half of the isathergic-immune animals. The quantitative data are presented in Table 4 and will be discussed later.

Thus we have demonstrated experimentally that *tuberculo-anaphylaxis, tuberculo-allergy and tuberculo-immunity can be produced concomitantly in one and the same animal organism and that subsequent production of antianaphylaxis and tuberculin anergy is possible of accomplishment without the abolition of tuberculo-immunity*. This statement is supported by our previous (1941) demonstration that repeated injections of BCG-tuberculo-protein fail to immunize guinea pigs against a virulent tuberculous infection, and that allergy invariable develops after the injection of dead or living tubercle bacilli. The successive elimination of anaphylaxis and allergy must, therefore, of necessity leave tuberculo-immunity behind intact.

The following experiments will prove that antianaphylaxis fails to remove allergic hypersensitiveness and that the latter is not essential for the production of immunity, although it may co-exist with a certain degree of immunity.

Tuberculo-anaphylaxis in allergic-immune animals. — Table 5 presents the essential quantitative data on six allergic-immune group II animals which had been anaphylactically sensitized with

Table 3.

Tuberculo-Anaphylaxis in Isathergic-Immune Tuberculous Guinea Pigs.

Animal No.	Tuberc. shock dose mg	Death Min.	Degree Tbc.	Body Wt. gm	Quantitative Visceral Data						
					L u n g s			Liver	Spleen	Glands	
										Mesent.	Total
					Gm	MI	Ratio	Gm	Gm	MI	Gm
D—840	0.96	4	+	560	5.2	16.2	1: 3.19	29.5	1.5	0.65	5.0
D—841	0.96	5	+	505	8.8	20.0	1: 2.27	38.0	1.8	0.43	4.6
D—845	2.88	7	++	590	10.4	25.0	1: 2.40	33.5	1.5	0.68	3.2
D—861	3.84	4	±	580	8.5	16.0	1: 1.88	38.0	0.8	0.47	3.5
D—867	4.80	5	±	540	5.1	14.5	1: 2.77	34.5	0.6	0.53	5.3
D—868	4.80	7	++	400	7.0	15.0	1: 2.14	36.5	1.4	0.64	7.1
Average				529	7.5	17.5	1: 2.33	35.0	1.3	0.57	4.8

Table 4.

Tuberculo-Antianaphylaxis and Tuberculin Anergy in Iathergic-Immune Tuberculous Guinea Pigs.

Animal No.	Tubprot. shock dose mg	Killed	Degree Tbc.	Body Wt. gm	Quantitative Visceral Data						
					L u n g s			Liver	Spleen	Glands	
					Gm	Ml	Ratio	Gm	Gm	Mesent. Total	
		Hts.								Ml	Gm
D-847	0.096 × 10	16 ¹	++	450	5.6	7.0	1: 1.25	28.5	0.9	0.67	3.4
D-848	0.096 × 10	16 ¹	++	420	7.7	10.0	1: 1.30	31.0	1.4	0.57	4.4
D-849	0.096 × 10	16 ¹	±	625	10.8	9.5	1: 0.88	54.5	0.9	0.58	5.2
D-864	» » +2.88	24 ²	±	550	7.5	11.0	1: 1.47	37.5	0.9	0.38	6.0
D-846	» » +4.80	16 ²	±	490	6.7	8.0	1: 1.19	41.5	1.0	0.55	2.5
D-850	» » +4.80	16 ²	+	440	10.2	11.5	1: 1.13	35.0	1.4	0.19	3.0
Average				493	8.1	9.5	1: 1.12	38.0	1.1	0.49	4.1
Total average (12)				513	7.8			36.5	1.2	0.53	4.4

tuberculo-protein, immunized with BCG and infected intraperitoneally with virulent tubercle bacilli. In order to prove the presence of anaphylactic sensitization in this group, an assaulting dose of 0.96 to 4.80 mg specific tuberculo-protein was injected intravenously in the jugular vein. All the six animals succumbed in acute anaphylactic shock within 3 to 7 minutes later. The data on the lungs are essentially those described under the anaphylactic death in iathergic-immune animals, namely an increased weight and volume ratio from the normal 1: 1.2 to 1: 2.83. The most conspicuous pathological difference between these and the iathergic-immune animals was the advanced degree of visceral tuberculosis, with one +++ and five ++++ generalized tuberculosis. The weight of the spleen and mesenteric lymph glands was 5 times greater than those recorded in the iathergic-immune group and that of the total lymph glands is the double. We shall return to the discussion of these quantitative differences later.

Antianaphylaxis and allergic death in allergic-immune animals.

— In this phase of our experiments we find the counterpart to the

¹ Transient anaphylactic shock early in process of desensitization, recovered, remained well. Killed 16—24 hours later (proof of complete or nearly complete tuberculin anergy, i. e. iathergy).

² Violent anaphylactic shock early in process of desensitization, recovered and remained well. Killed 16—24 hours later.

tuberculin energy which we observed in the antianaphylactic iathergic-immune animals (vide Table 4). The data given in Table 6 are drawn from the six allergic-immune animals which remain in group II. It will be recalled that these animals have received the same preparatory treatment as the iathergic-immune animals in Table 4 except that these allergic-immune animals have not been desensitized allergically with tuberculin. Antianaphylaxis was attempted in these animals in exactly the same manner as in the iathergic-immune animals in Table. But the conspicuous feature is that every one of these allergic-immune animals developed fatal tuberculin intoxication within 10—12 hours after the intravenous injection with 0.096×10 mg specific tuberculo-protein plus 2.88 or 4.80 mg. Autopsy revealed excessive exudations in the serous cavities and extensive hemorrhages in the viscera, especially in the liver and the spleen. Two animals presented ++ tuberculosis, two +++ and two ++++ generalized tuberculosis. A glance at Tables 3—4 and 5—6 reveals at once the more excessive tuberculous hyperplasia in the viscera of the allergic-immune than of the iathergic-immune animals. But we shall return later to the quantitative evaluations of the organic changes in this group. Thus we have demonstrated that *the abolition of tuberculo-anaphylaxis in the allergic-immune tuberculous animals is accomplished only at the risk of producing fatal allergic intoxication, and that allergic hypersensitiveness is not essential for the development of tuberculo-immunity.*

Table 5.

Tuberculo-Anaphylaxis in Allergic-Immune Tuberculous Guinea Pigs.

Animal No.	Tubprot. shock dose mg	Death Min.	Degree Tbc.	Body Wt. gm	Quantitative Visceral Data						
					L u n g s			Liver	Spleen	Mesent. Glds.	Total Glds.
					Gm	Ml	Ratio	Gm	Gm	Ml.	Gm
A—839	0.96	4	++++	400	8.8	17.0	1: 1.93	48.5	9.0	0.39	5.9
A—853	0.96	4	++++	370	6.5	18.8	1: 2.89	35.0	5.1	3.00	4.6
A—862	2.88	5	++++	400	6.7	16.5	1: 2.46	43.0	9.0	3.40	12.9
A—863	3.84	3	+++	500	5.7	16.0	1: 2.81	33.5	7.2	3.30	12.4
A—873	3.84	7	+++	400	6.0	18.5	1: 3.08	42.5	3.4	0.51	8.0
A—872	4.80	4	++++	380	5.1	19.5	1: 3.82	41.0	6.6	1.30	9.7
Average				408	6.5	17.7	1: 2.83	40.6	6.7	1.98	8.9

Table 6.

Tuberculo-Antianaphylaxis and Allergic Death in Allergic-Immune Tuberculous Guinea Pigs.

Animal No.	Tubercul. shock dose mg.	Death	Degree Tbc.	Body Wt. gm.	Quantitative Visceral Data						
					L u n g s			Liver	Spleen	Mesent. Glds.	Total Glds.
					Gm	Ml	Ratio	Gm	Gm	Ml	Gm
A-842	0.096 × 10	12	+++	430	5.2	10.0	1: 1.92	34.0	2.0	0.97	5.0
A-851	0.096 × 10	12	++++	540	7.1	11.0	1: 1.55	35.0	2.1	7.80	22.8
A-852	0.096 × 10	10	++++	370	5.9	6.5	1: 1.10	35.5	3.6	3.10	8.5
A-854	0.096 × 10										
	+2.88	10	++	620	7.7	11.5	1: 1.50	31.5	1.1	2.00	6.6
A-855	0.096 × 10										
	+4.80	10	++	660	8.9	10.0	1: 1.12	36.5	0.9	3.70	9.0
A-869	0.096 × 10										
	+4.80	12	+++	340	5.5	8.5	1: 1.55	40.5	3.8	1.30	5.2
Average				493	6.7	9.6	1: 1.46	35.5	2.3	3.14	9.5
Total average (12 animals)				451	6.6			38.0	4.5	2.56	9.2

Tuberculo-allergy in control animals. — Table 7 presents the quantitative data on twelve control tuberculous guinea pigs. Two of these died spontaneously with +++ and ++++ generalized tuberculosis. The remaining ten animals were injected intravenously in the jugular vein with 0.96 to 4.80 mg. BCG-tuberculo-protein. In none of these animals was acute anaphylactic shock produced, but every one died 7 to 12 hours later in protracted allergic intoxication. Autopsy revealed extreme semi-sanguinous exudations into the serous cavities and extensive hemorrhages in the liver, spleen, lungs and lymphatic glands, especially in the mesentery and omentum, besides fulminating general tuberculosis, with multiple and large infarcts in the spleen and the liver, cavernous tubercles in the lungs and heavy fibrocaseous hyperplasia of the lymph glands. A perusal of the quantitative data in Table 7 reveals that the spleen is nearly 6 times greater in weight than that in the iatbergic-immune group, and that the total lymphatic glands weigh 4 times more than those in the iatbergic-immune group. It is apparent that the tuberculous changes in the allergic-immune animals hold an intermediate position between those recorded for the control and

iathergic-immune animals. The quantitative data of the experiments recorded above have now placed us in position to evaluate the immunizing effect of the BCG-paraffin focus on the virulent infection with human tubercle bacilli in tuberculin anergic or allergic organisms.

Table 7.

Non-Anaphylactic Allergic Death in Control Tuberculous Guinea Pigs.

Animal No.	Tuberc. shock dose mg	Death hours	Degree Tbc.	Body weight gm	Quantitative Visceral Data						
					L u n g s			Liver	Spleen	Mesent. Glds.	Total Glds.
					Gm	MI	Ratio	Gm	Gm	MI.	Gm
C-838	—	Spont.	+++	320	8.5	10.5	1: 1.24	22.4	2.3	1.43	6.7
C-844	—	Spont.	++++	320	7.2	9.0	1: 1.25	29.0	14.3	0.43	6.2
C-856	0.96	7	++++	250	6.0	8.0	1: 1.33	28.5	7.7	2.90	7.2
C-857	0.96	9	++++	360	9.5	13.0	1: 1.37	37.0	9.1	6.90	18.5
C-858	0.96	7	++++	480	7.0	9.5	1: 1.36	46.7	6.0	13.10	30.0
C-870	0.96	12	++++	530	8.2	12.5	1: 1.52	65.0	8.1	15.50	24.3
C-871	0.96	12	++++	560	7.3	10.0	1: 1.37	57.0	4.3	6.10	18.7
C-859	1.92	10	++++	480	8.5	11.0	1: 1.29	42.0	3.2	13.00	24.2
C-860	1.92	12	++++	480	8.7	11.0	1: 1.26	44.5	3.1	3.90	13.5
C-865	2.88	8	++++	510	6.9	8.5	1: 1.23	41.5	1.8	7.30	22.0
C-866	2.88	12	++++	508	8.1	8.5	1: 1.05	57.0	11.5	5.20	22.3
C-843	4.80	12	++++	400	10.5	14.0	1: 1.33	52.5	10.1	8.50	20.5
Average				432	8.0	10.5	1: 1.29	43.6	6.8	7.02	17.8

Quantitative assessment of tuberculo-immunity.

Our previous experience has taught us that the most exact method for determining the tuberculous hyperplastic changes which take place in the lymphatic glands is by the water displacement apparatus already described (1940). The smallest of these apparatus is calibrated down to 0.001 ml. The data in Table 8 are collected by means of these apparatus. The weight of the spleen, liver, lungs and the pooled (total) lymphatic glands is known to vary according to the body weight of the animal. In Table 9 we have therefore converted these weights into the more exact percent of the animal's body weight. The completed data are subsequently submitted to statistical analysis according to Fisher's (1936) method for comparison of two comparable means (x) and (y). In our present study we

have chosen to reject as insignificant any mean value of P (probability) which is more than 0.01. The symbol $P \leq 0.01$ signifies, therefore, that the observed mean deviations bearing this or smaller values must be considered to have *absolute statistical significance* and cannot have occurred by chance alone. In Fisher's 1938 tables for distribution of t (symbol signifying how much greater the difference between x and y is than their standard error), a $P \leq 0.01$ requires that $t \geq 2.819$ when each group contains 12 animals or samples. Every difference having *absolute significance* is italicised in Tables 8 and 9. »Sigma» or the *standard deviation* (square root of the arithmetic mean of the squares of the deviations from the average) enables one to follow the actual dispersion from the average within the group. This measure gives more weight to extreme cases than other measures of variability. By this cumbrous and carefully planned quantitative procedure we have endeavoured to assess as objectively as possible the degree of tuberculous hyperplasia as it occurs in the iathergic-immune, allergic-immune and control animals. We are guided in this respect by Lord Kelvin's classical remarks that »when you can measure what you are speaking about and express it in numbers, then you know something about it. But when you cannot measure it, nor express it in numbers, your knowledge is of a meagre and unsatisfactory kind.»

Volume of lymph glands. — The volumetric data on the most representative lymph glands in the guinea pig organism are given in Table 8. We are at once struck by the nearly normal volumes of the lymph glands in the iathergic-immune group I animals, the moderately enlarged volumes in the allergic-immune group II animals, and the excessively hyperplastic lymphatic glands in the control group III animals. When the volumetric data of the iathergic-immune group are compared with those of the control group (I vs III), we find that 11 out of 16 lymphatic glands show differences of absolute statistical significance, or an efficiency of 68.8 percent in favour of the higher tuberculo-glandular resistance in the iathergic-immune animals. The comparison of the glandular volumetric data in the allergic-immune group with those in the control group (II vs III) reveals that only 3 out of 16 lymphatic glands show differences of absolute statistical significance, or an efficiency of only 18.8 percent in favour of a higher glandular

tuberculo-resistance in the allergic-immune than in the control animals. Plates I—III depict demonstratively the apparent differences in the excessive fibrocaceous lymph glands in the control group, the relative hyperplasia in the allergic-immune group and the nearly normal appearance of the lymph glands in the iathergic-immune group. The most conspicuous differences obtain in the mesenteric glands which bear the greatest brunt of the intraperitoneal inoculation with virulent tubercle bacilli.

Weight of total lymph glands. — When the lymphatic glands enumerated in Table 8 are pooled and weighed as »total glands» converted into percent of the animal's body weight, as stated in Table 9, we find that the difference between the iathergic-immune and control groups is nearly 8 times greater than their standard

Table 8.

Tuberculous Hyperplasia in Lymph Glands

Statistical analyses of volume (in ml) of lymph glands from (I) iathergic-immune, (II) allergic-immune, and (III) control tuberculous guinea pigs. (12 animals in each group).

Glands	I. Iatherg.-Immune		II. Allerg.-Immune		III. Control		P r o b a b i l i t y			
							I vs III		II vs III	
	Av.	Sigma	Av.	Sigma	Av.	Sigma	<i>t</i>	<i>P</i>	<i>t</i>	<i>P</i>
Sup. Inguin. Lf.	0.270	0.135	0.440	0.217	0.620	0.370	2.810	0.01	1.328	0.20
» » Rt.	0.290	0.086	0.240	0.151	0.560	0.320	2.582	0.02	2.859	< 0.01
Femoral Lf.	0.120	0.044	0.350	0.190	0.280	0.155	3.160	< 0.01	0.902	0.35
» Rt. ..	0.110	0.048	0.270	0.113	0.300	0.160	2.744	0.015	0.483	0.65
Periportal	0.370	0.132	0.860	0.605	1.090	0.606	3.667	< 0.01	0.848	0.40
Mesenterial	0.530	0.137	2.560	1.950	7.020	4.586	4.694	< 0.001	2.967	< 0.01
Trach-bron. Lf. ...	0.280	0.124	0.720	0.464	0.720	0.270	4.687	< 0.001	0.000	> 0.96
» » Rt. ...	0.270	0.120	0.510	0.289	0.620	0.105	3.129	< 0.01	0.646	0.52
Cervical Lf.	0.100	0.034	0.240	0.122	0.250	0.123	3.729	< 0.01	0.201	0.85
» Rt.	0.100	0.040	0.246	0.166	0.280	0.119	4.535	< 0.001	0.620	0.55
Axillary Lf.	0.130	0.052	0.200	0.136	0.300	0.107	4.501	< 0.001	1.828	0.08
» Rt.	0.120	0.067	0.130	0.067	0.230	0.099	2.874	< 0.01	2.634	0.02
Knee Lf.	0.035	0.016	0.090	0.065	0.060	0.036	2.008	0.06	1.289	0.25
» Rt.	0.035	0.013	0.050	0.037	0.060	0.042	1.807	0.08	0.570	0.55
Deep Ing. Lf. ..	0.065	0.052	0.080	0.058	0.110	0.053	1.921	0.07	1.205	0.25
» » Rt. ..	0.050	0.045	0.037	0.024	0.080	0.037	1.633	0.11	3.097	< 0.01

Statistically significant deviations from the comparable group appear in *italics*. Values shown in ordinary type proved not to be statistically significant deviations from the comparable group.

Fig. 2

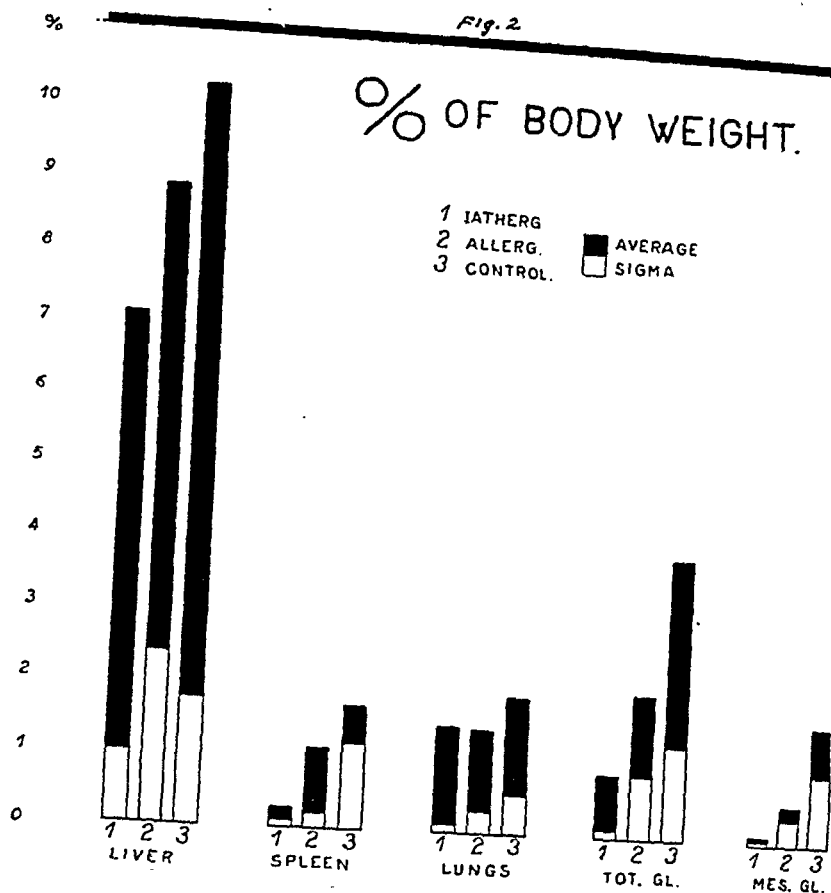


Chart 2. Average Weight of Liver, Spleen, Lungs, Mesenteric and Total Lymph Glands, expressed in Percent of Body Weight.

error. This gives a $P \leq 0.001$, a figure of incontestable statistical significance in favour of the higher glandular tuberculo-resistance in the iathergic-immune than in the control animals. That the allergic-immune group II animals also possess a moderate degree of glandular tuberculo-resistance is evident from the fact that the difference between this group and the control group is 4 times greater than their standard error. This gives also a $P \leq 0.001$ which bespeaks absolute significance.

Should we content ourselves with the quantitative data on the lymph glands alone, we would possess adequate proof of the nearly complete protection of the iathergic-immune state against tuberculosis in the lymph glands. But we would also have proof that the state of allergic hypersensitiveness dissipates a great deal of the

immunity which is acquired through the BCG-paraffin premunition. Hence we may conclude that even as we have dissociated tuberculo-anaphylaxis from tuberculo-allergy in one and the same animal organism, we have also dissociated tuberculo-immunity from the two before mentioned biological phenomena on the basis of a nearly complete tuberculo-resistance in the glands of the iathergic-immune animals.

Weight of spleen, liver and lungs. — The weight of the spleen, liver and lungs was converted into percentage of the animal's body weight and these data are presented in Table 9. It is well to recall the statement by Allan K. Krause (1919) that *»in the guinea pig . . . the spleen is undoubtedly the organ that is most prone to tubercle.»* Thus we find that the weight of the spleen in the iathergic-immune group was only 0.340 percent of the body weight while it was 1.740 percent in the control group. The difference between these two groups was found to be 4.79 times greater than their standard error, or of absolute significance ($P \leq 0.001$). The difference between the 1.1 percent splenic weight in the allergic-immune group and the 1.74 percent in the control group fell short of any significance ($P = 0.15$). By this same procedure, the weight of the liver in the iathergic-immune group was found to be 7.68 percent of the body weight while the weight of the liver in the control group was 10.383 percent. The difference between these two weights was more than 5 times their standard error, or of absolute significance ($P \leq 0.001$). The weight of the allergic-immune liver was 8.911 percent of the body weight and failed to differ significantly from that of the control group. The weight of the lungs in the iathergic-immune group was 1.54 percent of the body weight while it was 1.95 percent in the control group. The difference between these two weights was 2.156 times greater than their standard error, but this gives a $P = 0.04$, which, although it falls within the limit of significance (twice the standard error) it does not place any high degree of confidence (i. e. $P = 0.01$) on the results (vide Fisher, 1936, pp. 121 and 131). The same holds true for the difference in the weight of the lungs in the allergic-immune and the control groups.

The photographs of the lungs, liver and spleen from two animals in each of the three groups under discussion (Plates I—III) depict clearly the marked differences in macroscopic tuberculous lesions in these animals.

RECORD OF RECORD

Section No. 099
 Animal No. D. 7
 Sex Male
 Date of birth 11/22-41
 Weight 550
 Days of survival 580
 Days of record 580

Lungs:



Liver:



Spleen:



1

RECORD OF RECORD

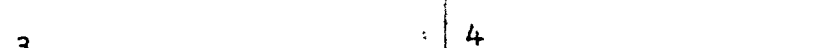
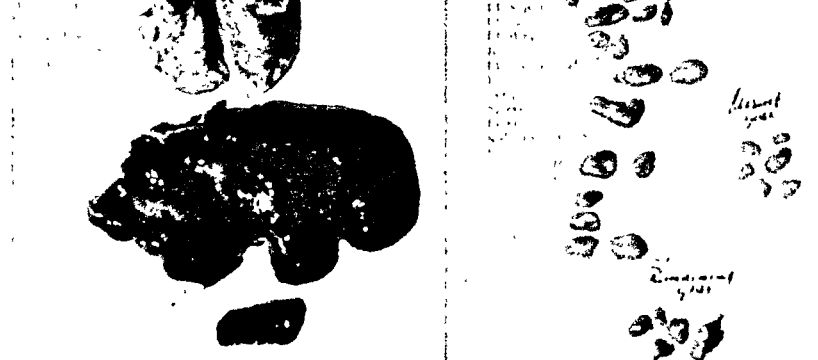
Section No. 361
 Animal No. D. 9
 Sex Male
 Date of birth 11/22-41
 Weight 580
 Days of survival 580
 Days of record 580



3

RECORD OF RECORD

Section No. 361
 Animal No. D. 9
 Sex Male
 Date of birth 11/22-41
 Weight 580
 Days of survival 580
 Days of record 580



2

4

AUTOPSY RECORD

Section No. 337

Autopsy No. K-5

Sex

Race

Date of survival

Description

H. section 1/2

H. K. 1/2

H. 1/2

H. 1/2

H. 1/2

H. 1/2

H. 1/2

H. 1/2

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DIAGNOSIS

Hemorrhagic infarction
of the brain

9

AUTOPSY RECORD

Section No. 338

Autopsy No. K-6

Sex

Race

Date of survival

Description

H. section 1/2

H. K. 1/2

H. 1/2

H. 1/2

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DIAGNOSIS

11

AUTOPSY RECORD

K-5

Section No. 337

Autopsy No. K-5

Sex

Race

Date of survival

Description

H. section 1/2

H. K. 1/2

H. 1/2

H. 1/2

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H. 1/2

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12

Thus, the significant findings in the lymph glands are repeated in the quantitative analyses of the spleen, liver and lungs. This permits us to conclude that the highest degree of tuberculo-resistance is abundantly present in the iathergic-immune animal organism which is barred from becoming allergic hypersensitive neither during the period of immunization nor during the virulent superinfection. Furthermore, it is quite apparent that acquired tuberculo-resistance is greatly dissipated in the state of allergic hypersensitivity which, in the words of S. Lyle Cummins (1939) is »the shadow but not the substance of immunity, (which) is drawn across the picture and leads, or has led, to a great deal of confusion.»

Table 9.

Tuberculous Hyperplasia in Spleen, Liver, Lungs and Total Lymphatic Glands.
Statistical analysis of weight of spleen, liver, lungs and total lymphatic glands expressed in percent of the animal's body weight (12 animals in each group).

Organs	I. Iatherg-Immune		II. Allerg.-Immune		III. Control		P r o b a b i l i t y			
							I vs III		II vs III	
	Av. %	Sigma	Av. %	Sigma	Av. %	Sigma	t	P	t	P
Spleen ..	0.240	0.088	1.100	0.223	1.740	1.200	4.790	< 0.001	1.522	0.15
Liver ..	7.180	1.094	8.911	2.372	10.383	1.770	5.096	< 0.001	1.644	0.14
Lungs ..	1.540	0.121	1.490	0.286	1.950	0.521	2.156	0.04	2.619	0.017
Glands..	0.890	0.103	2.046	0.882	3.990	1.300	7.669	< 0.001	4.118	< 0.001

Viable tubercle bacilli in the spleen. — It is agreed that the highest function of acquired immunity is to localize and to destroy invading virulent microbes. We have already emphasized the excessive vulnerability of the guinea pig spleen for tubercle bacilli. It was decided therefore to determine by culture the number of viable tubercle bacilli which might be present in the entire spleen in half of the animals in each of the three groups. Because of the uniform smallness of the spleen removed from the iathergic-immune animals (0.7—1.5 g), the entire organ was cultured from 6 animals in this group. The size of the spleen taken from the 6 allergic-immune and 6 control animals was so large (2.1—11.5 g) that we found it inconvenient to employ the entire organ. Approximately 1 g of the spleen was therefore removed from each of these animals for culture. The method of the bacterial technique was the same as we have pre-

Table 10.

Distribution of viable tubercle bacilli in the spleen of iathergic-immune, allergic-immune and allergic-control guinea pigs.

Animals		Spleen		Colonies of tubercle bacilli in				
Group	Nr	Total weight gm	Weight cultured gm	Dilutions				Estimated in total spleen
				1/10	1/100	1/1000	1/10,000	
Iathergic-Immune	D—3	1.5	1.5	138	14	2	0	1,380
	D—4	1.0	1.0	20	1	0	0	200
	D—5	0.9	0.9	3	0	0	0	30
	D—6	1.4	1.4	264	25	2	0	2,640
	D—8	1.4	1.4	206	19	1	0	2,060
	D—9	0.7	0.7	42	2	0	0	420
Total:		6.9	6.9	673	61	5	0	6,730
Allergic-Immune	A—3	2.1	1.1	∞	∞	34	4	64,910
	A—4	3.6	0.9	124	12	2	0	4,960
	A—5	5.1	1.3	∞	∞	113	10	443,307
	A—8	9.0	1.0	∞	∞	126	14	1,134,000
	A—9	7.2	1.0	∞	43	6	0	30,960
	A—10	3.8	1.1	∞	∞	68	8	234,910
Total:		30.8	6.4	∞	∞	349	36	1,913,047
Allergic-Control	K—4	7.7	1.0	∞	∞	96	14	739,200
	K—5	9.1	1.1	∞	∞	311	29	2,572,736
	K—6	6.0	1.1	∞	∞	23	5	125,455
	K—7	3.2	1.0	∞	∞	53	6	169,600
	K—8	3.1	1.0	∞	∞	38	4	117,800
	K—10	11.5	1.0	∞	264	18	2	303,600
Total		40.6	6.2	∞	∞	539	60	4,028,391

Calculated tubercle bacilli per 1 gm. splenic tissue:

In iathergic-immune group = 975.
 In allergic-immune " = 62,112.
 In allergic-control " = 99,221.

viously described (1940), namely of making serial dilutions in saline of the alkali-acid treated homogenized splenic tissue. This was subsequently seeded out on 50 ml tubes of Löwenstein's solid egg medium. After 8 weeks incubation at 37.5° C., we counted the eugonic colonies of human tubercle bacilli. The data of these bacterial cultures are given in Table 10. It will be seen that the estimated viable tubercle bacilli (colonies) contained in the entire spleen

varied from 30 to 2,640 in the iathergic-immune animals, or an average of 975 tubercle bacilli per 1 g of splenic tissue. In the spleens removed from the allergic-immune animals the bacillary counts varied from 4,960 to 1,134,000, or an average of 62,112 bacilli per 1 g of splenic tissue. In the control spleens the count varied from 117,800 to 2,572,736 bacilli, or an average of 99,221 bacilli per 1 g of splenic tissue. The high degree of tubercle bacillus bacteriostasis in the iathergic-immune splenic tissue explains the general inhibition of tuberculous hyperplasia in the liver, lungs and lymphatic glands in these animals and contrasts well with the relatively abundant growth of tubercle bacilli in the allergic-immune animals. This reconfirms our previous bacteriostatic investigations in iathergic-immune organisms (1940).

Discussion.

The separability of tuberculo-anaphylaxis and tuberculo-allergy is widely accepted while the separability of tuberculo-allergy and tuberculo-immunity appears to meet with scepticism in many quarters. Repeated citations of the recent study by Willis and Woodruff (1938) is an example of the inveterate belief that immunity in tuberculosis cannot exist in the complete absence of allergic hypersensitiveness. It will be recalled that these authors found that if desensitized animals are permitted to die from their reinfection with virulent tubercle bacilli, they survive a shorter period, develop more extensive pulmonary disease, and harbour larger numbers of viable tubercle bacilli in their internal organs than the allergic hypersensitive animals similarly reinfected but not desensitized. We have repeatedly (1937—1940) failed to confirm these observations. On the contrary, in resorting to careful quantitative assessment of the degree of visceral tuberculosis, we have found that the allergic desensitized animals resist virulent reinfection far better than allergic hypersensitive animals. However, the difference between the results of desensitization in the series by Willis and Woodruff and by us, is mostly explained by the fact that while our desensitizing doses never exceeded 250 mg tuberculin every other day in our first and second series and 200 mg thrice weekly in the following series, Willis and Woodruff resorted to the daily injection of 1000 mg tuberculin during 6 months. These excessive doses of tuberculin

contained, besides the specific tuberculo-protein, high concentrations of glycerin. We recall that Long and Vorwald (1930) had observed that tubercle bacilli grew more abundantly in rats treated with glycerin than in untreated control animals. That glycerin may not be the sole factor in the results obtained by Willis and Woodruff is apparent from the studies by Follis (1938) and by us (1937—1940) in which identical pneumonic lesions occurred in the allergic desensitized, allergic hypersensitive as well as in the control animals. Although Willis and Woodruff are inclined to believe that allergy and immunity are more closely related than we are willing to admit, yet their experiments prove only that immunity is less, but not lacking in the allergic desensitized (iathergic-immune) state. Even if the immune state which is shorn of allergic hypersensitiveness breaks down more rapidly during the virulent reinfection, the fact remains that the desensitized iathergic state is still more or less an immune state which differs from the state of the unprotected control animals in being nearer to immunity than they are. This expression of faith, as S. Lyle Cummins (1939) puts it, brings the view of Willis and Woodruff more or less into line with the view which Rich and his colleagues (1929—1934) and we (1937—1939) have advanced, though, unfortunately, they are so expressed as to appear far apart. In other words, Willis and Woodruff are obliged to acknowledge some immunity in their desensitized iathergic animals while we, even if our theory of complete separation of allergy and iathergy is questioned, still have established immunity in our completely or nearly completely desensitized iathergic animals. It is apparent, however, that a close approximation exists between our views inasmuch as Woodruff admits in a personal communication (1939) that »by employing smaller doses of tuberculin for desensitization purposes», he too has observed »beneficial effect on the course of a tuberculous infection.» This proves Claude Bernard's statement (1859) »that experiments are rigorous and give identical results wherever we operate in exactly similar conditions.»

In our present study of the concurrent development and alternate dissociation of tuberculo-anaphylaxis, tuberculo-allergy and tuberculo-immunity in one and the same animal organism, we found it necessary to repeat the comparative analysis of the behaviour of the tubercle bacilli of reinfection in the completely or nearly completely desensitized iathergic-immune animals and in

clude that an effective resistance can be produced against a virulent reinfection in the complete absence of allergic hypersensitiveness.

It is clear, therefore, that what we have inferred from earlier investigations on the separability of tuberculo-allergy and tuberculo-anaphylaxis on the one hand, and tuberculo-allergy and tuberculo-immunity on the other hand, has now found suggestive confirmation in our successful attempt to produce concurrently and to dissociate alternately these three apparently characteristic and unrelated biological phenomena, in one and the same animal organism.

Besides the purely scientific inquiry into the causes and conditions which determine the character of the observed phenomena, we are inclined to believe that these studies will have definite connotation for the complete evaluation of the resistance against tuberculosis, as it is acquired by man. A series of clinical observations are already under redaction on the phenomenon observed by us (1941), and Thorkildsen (1942), of the persistence of iathergic-immunity in BCG-vaccinated persons who shortly afterwards become tuberculin negative, and yet respond to the cutaneous multiple puncture revaccination (ad modum Rosenthal), with an immediate defensive reaction. A comparison may likewise be drawn between iathergic-immunity and the state of »positive anergy» (negative tuberculin test) which always accompanies the clinical entity *Lymphogranulomatosis benigna* (Boeck's sarcoid), a condition which deserves a more extensive experimental investigation than the commendable attempt recently made by Lemming (1940).

Summary and Conclusions.

1. Tuberculo-anaphylaxis, tuberculo-allergy and tuberculo-immunity have been produced concurrently in one and the same animal organism and alternately separated as characteristic and apparently unrelated biological phenomena.

2. Purified tuberculoprotein possesses high tuberculin activity, is non-toxic for normal guinea pigs, sensitizes anaphylactically but not allergically and fails to immunize against virulent tuberculous infection.

3. Elimination of tuberculo-anaphylactic hypersensitiveness by production of non-fatal anaphylactic shock (antianaphylaxis) fails to remove or impair tuberculo-allergic hypersensitiveness.

4. Elimination of tuberculo-allergic hypersensitiveness by sustained desensitization with tuberculin, fails to remove or impair tuberculo-immunity which may be maintained in the complete absence of allergic-hypersensitiveness.

5. Intravenous injection of lethal amounts of tuberculoprotein or tuberculin in completely desensitized iathergic-immune guinea pigs infected with virulent tubercle bacilli, fails to produce allergic intoxication (crucial test of complete desensitization).

6. Localization and destruction of virulent tubercle bacilli in reinfection is significantly more effective and complete in the desensitized iathergic-immune than in the hypersensitive allergic-immune guinea pigs.

7. Inhibition of visceral tuberculosis following the intraperitoneal inoculation with virulent human tubercle bacilli is most effective in the completely desensitized iathergic-immune guinea pigs while much of the acquired tuberculo-immunity is dissipated in the hypersensitive allergic state.

8. The three tuberculo-biological phenomena of anaphylaxis, allergy and immunity appear to disclose distinguishing characteristics which separate them as independent phenomena.

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Explanation of plates.

Plate 1.

Fig. 1. Desensitized iathergic-immune guinea pig D 849, given 0.096 mg purified tuberculoprotein intravenously every minute during 10 minutes. Violent transient anaphylaxis with recovery (antianaphylaxis). Developed no allergic intoxication during the following 16 hours (*completely desensitized allergically*). Killed. Note absence of organic tuberculosis in lungs, liver and spleen.

Fig. 2. Ibid. Lymphatic glands show normal appearance. Total weight of glands 5.2 g. Glands arranged from above downwards in following order: left (1) and right knee (1); lf. (3) and rt. sup. inguinal (3); lf. (1) and rt. deep. inguinal (1); lf. (1) and rt. femoral (1); periportal (1); lf. (1) and rt. tracheo-bronchial (1); lf. (1) and rt. cervical (1); lf. (1) and rt. axillary (1); mesentery (on the right) and remaining (retro-renal and sternal, etc.) (below).

Fig. 3. Desensitized iathergic-immune guinea pig D-861, given 3.84 mg purified tuberculoprotein intravenously. Died in 4 minutes in anaphylactic shock. Note absence of organic tuberculosis. Lungs are hugely expanded, weigh 8.5 g and measure 16 ml (ratio 1: 1.88; normal 1: 1.12).

Fig. 4. Ibid. Lymphatic glands show normal appearance. Total weight of glands 3.5 g.

Plate 2.

Fig. 5. Hypersensitive allergic-immune guinea pig A-862, given 2.88 mg purified tuberculoprotein intravenously. Died in 5 minutes in anaphylactic shock. Note generalized +++ organic tuberculosis. Lungs are widely expanded, weigh 6.7 g and measure 16.5 ml (ratio 1: 2.46).

Fig. 6. Ibid. Lymphatic glands show marked caseo-fibrous tuberculous hyperplasia. Total weight of glands 12.9 g.

Fig. 7. Hypersensitive allergic-immune guinea pig A-863, given 3.84 mg purified tuberculoprotein intravenously. Died in 3 minutes in anaphylactic shock. Note generalized +++ organic tuberculosis. Lungs are widely expanded, weigh 5.7 g and measure 16.0 ml (ratio 1: 2.81).

Fig. 8. Ibid. Lymphatic glands show marked caseo-fibrous tuberculous hyperplasia. Total weight of glands 12.4 g.

Plate 3.

Fig. 9. Control tuberculous guinea pig C-857, given 0.96 mg purified tuberculo-protein intravenously. Died 9 hours later in extreme allergic intoxication. Note generalized + + + + organic tuberculosis.

Fig. 10. Ibid. Lymphatic glands show marked caseous hyperplasia. Total weight of glands 18.5 g.

Fig. 11. Control tuberculous guinea pig C-858, given 0.96 mg purified tuberculo-protein intravenously. Died 7 hours later in extreme allergic intoxication. Note generalized + + + + organic tuberculosis.

Fig. 12. Ibid. Lymphatic glands show excessive caseo-necrotic tuberculous hyperplasia. Total weight of glands 30.0 g.

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(Chief: Professor, C. E. Bloch, M. D.) and from the Øresund Hospital
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Prothrombin Content of the Blood in Pulmonary Tuberculosis.

By

P. PLUM and JACOB E. POULSEN.

(Submitted for publication May 30, 1942).

Recently R. F. Sheely found a reduction of the prothrombin content of the blood in pulmonary tuberculosis. In 1941 Gyntelberg and Dam found that the prothrombin content, measured by Dam and Glavind's R-value method, was normal in the blood of 20 patients suffering from pulmonary tuberculosis; half of these patients had haemoptysis. From these observations they concluded that there was no basis for treating tuberculous haemoptysis patients with vitamin K.

Sheely's determinations were made with Quick's method and the results are given as the prothrombin content in percentage of the normal. In Quick's method the prothrombin time is determined in seconds, and Quick has given a »standardization curve» by which the prothrombin time should be convertible to percent of normal. Here it must be mentioned that Quick's procedure in the drawing of the standard curve has proved to be inapplicable. (On the problem of standardization see the investigations of Plum and Larsen). As Sheely says nothing of how his conversion curve is arrived at, it must be supposed that he employed Quick's procedure or the curve described by Quick. Un-

fortunately, variations in the prothrombin content in the blood between 50 and 100 per cent of normal will cause only slight fluctuations in the prothrombin time, as Quick's curve shows; with a prothrombin content of 100 per cent the time is about 13 seconds, and with 50 per cent it is about 15 seconds. As nothing is said in Sheely's paper of the error of each determination, and as the directly measured prothrombin times are not given, one cannot judge of the accuracy of the percentages given. Sheely's control material consists of an unstated number of persons whose prothrombin values are merely indicated as being over 90 per cent of normal.

Sheely found very close correlation between the prothrombin content in the blood and the degree and healing tendency of the tuberculosis; a normal prothrombin content was found in 73 per cent of the patients with minimal tuberculosis in 60 per cent with moderate and only 9.6 per cent with advanced stages. Of the most seriously affected group 68.5 per cent had a prothrombin content of less than 59 per cent of normal. In the group of 44 seriously affected patients it is seen that the prothrombin content in all cases are found between 20 and 69 per cent of normal, and that half of them had values between 40 and 49 per cent. Of 13 haemoptysis patients 8 had a prothrombin content of between 35 and 49 per cent of normal, which means a fairly considerable decrease. Vitamin K was given to four haemoptysis patients with a low prothrombin percentage; the prothrombin content of all four increased and the haemoptysis ceased, either on the same day or very soon afterwards. Sheely considers that the conclusion to be drawn from his investigations is that in certain cases of pulmonary tuberculosis, vitamin K may be an effective factor in the treatment of haemoptysis.

Own Investigations.

Method. The prothrombin determinations were made according to Plum and Larsen's modification of Quick's method. Venous blood was employed in every case, and no sample was used if there had been any difficulty in taking it. 1.7 cm³ blood was taken in a syringe containing 3.3 cm³ sodium citrate solution (0.03 g-sodium citrate, 0.078 g sodium chloride, distilled water to 10 cm³, stored in

sterile ampules) (two parts citrate solution to one part blood). The citrated blood was immediately transferred to a dry, sterile tube, thoroughly mixed, and the determination was made in the course of an hour after obtaining the blood. Ten determinations were made on every sample by an experienced assistant who knew nothing of the patients; the average of the ten determinations was employed. The prothrombin time was determined as follows: In a centrifuge tube is taken 0.3 cm^3 of the citrated blood and with a normal drop-pipette one drop (0.05 cm^3) of thrombokinase suspension is added, and finally 0.025 cm^3 of 1 per cent $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$. The determination is made at 37°C in a water-bath. The tubes are moved up and down about once per second, and the time ensuing from the addition of the calcium to the commencement of coagulation is taken with a stop-watch. The thrombokinase used is a non-dried human brain preparation ad modum Dam and Glavind, the contents of a frozen ampule of thrombokinase, 0.5 cc., being diluted with 1 cc. 0.9 per cent NaCl and then heated to 45°C in a water-bath for 15 minutes. The determinations were made in the period from January to March; fresh thrombokinase suspension was prepared every day and two different thrombokinase preparations were used (from two different brains); careful comparisons showed that the two preparations had the same activity.

When the prothrombin content of the blood is normal the prothrombin time is about 18 seconds; with decreasing prothrombin values the times increase, as the following table shows. These values have appeared as the result of numerous tests in which varying quantities of normal blood were added to patient blood very poor in prothrombin.

In order to test the accuracy of the method ten determinations were made on the same blood sample, each comprising ten individual determinations (100 in all), employing ten different thrombokinase suspensions from the same initial preparation. As the determinations were made on the same blood sample, the errors found do not involve errors originating from the blood sampling but only those concerned in the carrying out of the test itself and errors arising out of the different activities of the various thrombokinase ampules. Within the various series of ten determinations the maximum range was found to be from 0.8 to 1.8 seconds, averaging 1.24 seconds. The average of the series of ten-determinations varied

Table 1.

Relation between the prothrombin percentage and prothrombin time. Plum & Larsen's modification of Quick's method. Human brain trombokinase ad modum Dam & Glavind.

Prothrombin in percentage of the normal	Prothrombin time in seconds
100	18
50	26
20	50
10	90

from 18.10 to 18.87 seconds with a total average of 18.47 seconds. The standard deviation of the ten-determinations was found to be 0.276 second. It may therefore be assumed that the figures given below are subject to maximal error of $\pm 3 \times 0.276 = \pm 0.83$ sec.

Normal material. 50 normal individuals of ages from 20 to 55 years, 35 females and 16 males, were tested within the same period with the same thrombokinas preparations and in the same manner. The average for all 50 was 18.93 seconds, varying from 17.3 to 20.8 seconds. The average for females was 18.72 ± 0.84 seconds, for males 19.36 ± 1.02 seconds. The difference between the average for the two sexes is thus 0.64 second, and it was found to be 3.24 times greater than the probable error of the difference. This corresponds with Thordarson's investigations; he found that on an average the prothrombin content was a little higher in females than in males, about 3 per cent. The distribution of our normal material appears from the figure.

Patient material. The prothrombin content was determined in 101 patients suffering from pulmonary tuberculosis (66 males and 35 females); tubercle bacilli were demonstrated in all cases. The patients were in all stages of the disease, and there were 17 with haemoptysis. The average prothrombin time for all patients was 18.82 seconds, varying from 14.3 to 22.5 seconds. As the difference between the prothrombin times of normal males and females is so slight, sex has been disregarded in working up the patient material.

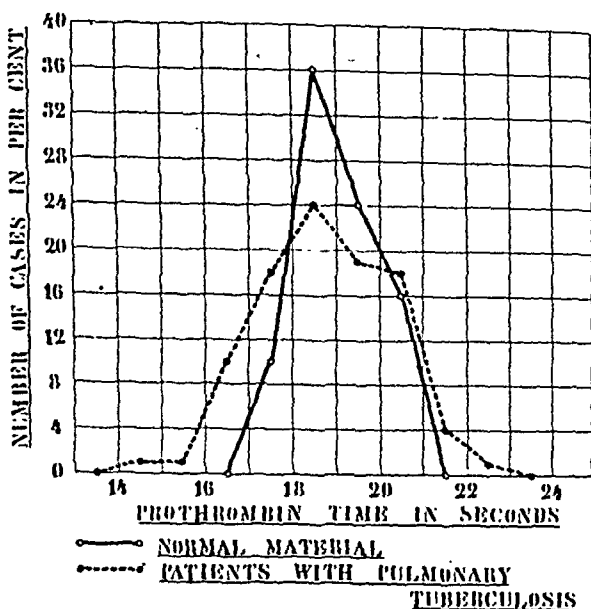


Fig. 1.

The patients are grouped according to the system used at the Øresund Hospital, in which the following criteria are employed: Temperature, weight, sedimentation rate, dyspnoea, and X-ray findings. The groups are:

I. »Good» *chronic cases*, for which the requirements are: a) no observed temperature increase during the past two months, b) weight not decreasing, c) sedimentation rate nearly constant, d) no dyspnoea from slight exertion, and e) X-ray reveals typical chronic process with retraction or non-typical process with unchanged picture for at least six months.

II. »Bad» *chronic cases*. X-ray results as in Group I, but with possible progression. The other requirements unsatisfied.

III. »Good» *non-chronic cases*. Duration less than six months. Points a) to d) as in Group I, but X-ray shows signs of fresh, not progressing process.

IV. »Bad» *non-chronic cases*. Duration less than six months. Points a) to d) unsatisfied. X-ray reveals signs of fresh, possibly progressing process.

Results. Group I (good chronic cases); 12 tests on 11 patients. Average 19 seconds, range 17.2 to 20.9 seconds.

Group II (bad chronic cases). 50 tests on 48 patients. Average 18.82 seconds, range 14.3 to 21.5 seconds.

Group III (good non-chronic cases). 15 tests on 15 patients. Average 19.34 seconds, range 17.2 to 21.6 seconds.

Group IV (bad non-chronic cases). 31 tests on 27 patients. Average 18.49 seconds, range 15.7 to 22.5 seconds.

Patients with haemoptysis. A total of 17 patients, who had had haemoptysis within the nine days previous to the tests were examined. The prothrombin time was 18.67 seconds on an average, varying from 14.3 to 21.0 seconds. Of the 17 patients 9 had haemoptysis on the day of the test, and for these the average prothrombin time was 18.77 seconds, varying from 14.3 to 21.0 seconds. Further the prothrombin values were compared to the sedimentation rate and the haemoglobin percentage, as shown in Table 2.

Table 2.

Prothrombin times compared with sedimentation rate.

Sedimentation rate (Westergren) mm in 1 hour	Prothrombin time seconds		Number of Patients
	Average	Range	
2—10	19.16	17.5—20.9	22
11—20	19.20	17.5—21.6	15
21—40	18.56	15.7—21.5	22
over 40	18.56	14.3—22.5	42

Only 7 patients had haemoglobin percentage of less than 85 per cent (100 per cent corresponding to an oxygen binding capacity of 18.5 volume per cent), viz. between 73 and 83 per cent. The average prothrombin time for these patients was 18.30 seconds, varying between 16.30 and 20.8 seconds.

Five of the patients died of their tuberculosis between 5 and 40 days after the blood sample was taken; four of them were nearly moribund of the day of the test. The average prothrombin time was 19.20 seconds, varying from 17.0 to 20.3 seconds.

Two patients had severe intrathoracal haemorrhage as a complication to an extra-pleural pneumothorax. The prothrombin times were 16.7 and 20.5 seconds respectively 5 days after and 3 weeks before the haemorrhage.

In 11 cases the prothrombin time was found to be exceptionally short i. e. less than 17 seconds. The only feature common to these patients is that they belong to the »bad» groups according to the Øresund Hospital system, viz. 4 bad non-chronic and 7 bad chronic. Of the latter two patients had haemoptysis. In 24 cases the prothrombin time was over 20 seconds. Of these, three patients were good non-chronic cases, 4 bad non-chronic, 4 good chronic and 13 bad chronic. Three of these 24 patients had haemoptysis, whereas 17 of all 101 patients had this complication. Accordingly, there does not seem to be any tendency to haemoptysis among patients with the longest prothrombin time (lowest prothrombin content), nor does a particularly short prothrombin time (high prothrombin content) prevent the occurrence of haemoptysis.

Administration of Vitamin K to Normal Individuals and to Patients with Pulmonary Tuberculosis with and without Haemoptysis. Four normal persons were given 100 mg 2-methyl-1.4-napthohydrokinondisuccinate (Synkavit) perorally, and the prothrombin time was determined before and 24 hours after ingestion by means of 10 tests in the same manner as described above. The prothrombin time decreased on an average 0.7 second., varying from 0.6 to 0.8 second, corresponding to a prothrombin increase of about 7 per cent. With prothrombin values in the normal range such a slight increase must be regarded as being of no importance to the coagulation of the blood.

Ten patients with pulmonary tuberculosis received 50 mg 2-methyl- 1.4-napthohydrokinondisulphate (Soluchinon) perorally. The prothrombin time was determined immediately before and 24 hours after ingestion. It was found that the prothrombin time decreased on an average 0.61 second., 7 patients recording a fall in the prothrombine time varying from 0.1 to 1.7 second., 2 patients were unchanged, and one patient rose by 1.0 second. Two of these ten patients had slight haemoptysis at the time of the test, continuing to the same degree on that day and the following ones, irrespective of the vitamin K ingestion.

Discussion. It will be seen from the foregoing that the content of prothrombin in the blood of the tuberculosis patients was found to be almost the same as in the normal material, the prothrombin time averaging 18.82 and 18.93 seconds respectively. It was also

found that the prothrombin time was a little shorter for the »bad» tuberculosis patients than for those who were improving, and that those with haemoptysis had a slightly shorter prothrombin time than the total average. In the tuberculosis material there was a somewhat greater scattering of the values than in the control material, but no values were found below 70 per cent of the normal prothrombin content. As we know that the prothrombin content must be reduced to less than 20—30 per cent of the normal before there is a tendency to haemorrhage on that account, it will be seen that in no case did we find a prothrombin reduction that, with our present knowledge, was of clinical significance.

From our material it might seem as if the patients most severely affected had the highest prothrombin concentration in the blood (the shortest prothrombin times); however, the difference observed may possibly have its explanation in the fact that these severe cases have a higher fibrinogen content in the blood than the less severe (higher sedimentation rate). As with the methode employed the plasma is diluted rather considerably, about 1: 6, it is possible that in the analysis the fibrinogen concentration comes nearer to the optimal when an increase of fibrinogen is found in the patient's blood.

The administration of very large doses of synthetic vitamin K to normal persons and to patients with pulmonary tuberculosis increased the prothrombin content in the blood with a few per cent. As the prothrombin was not found to be reduced below 70 per cent of the normal in any of the cases, such a slight increase must be assumed to be of no significance to haemoptysis and other haemorrhages.

Our investigations have thus given results which in every respect differ from those of Sheely. We are unable to find any explanation of the differences.

Conclusion. The present material has provided no indication for the use of vitamin K in cases of haemoptysis.

Summary.

1. The prothombin content in the blood of 101 patients with pulmonary tuberculosis was found to lie within the normal range when compared with a control material consisting of 50 healthy persons. The tests were made by means of Plum and Larsen's modification

of Quick's method on venous blood, 10 determinations being made on each blood sample. The accuracy of the method is examined.

2. The prothrombin content in the blood of 17 patients with haemoptysis was found to be normal.

3. The administration of large doses of synthetic vitamin K to 4 normal persons and 10 patients with pulmonary tuberculosis induced a very slight, probably unimportant, increase in the prothrombin content in the blood.

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Concerning negative tuberculin reactions in active pulmonary tuberculosis.

Does immunity persist in the absence of cutaneous allergy?

By

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(Submitted for publication August 17, 1942).

A tuberculin-negative person may become tuberculin-positive in the course of four to eight weeks after the exposure to tuberculous infection. It is a widespread belief that the allergic state comprises a corresponding immune state and that a positive tuberculin reaction is likewise a token of a relative acquired immunity against tuberculous infection. However, one may not deduct from a positive tuberculin reaction whether it is due to a clinically manifest tuberculosis or to an arrested process. A notable exception is infants where a positive tuberculin reaction is practically synonymous with the presence of active tuberculous disease. Thus, no parallelism exists between the tuberculin reaction and the strength and degree of the tuberculous disease, in spite of the fact that a stronger reaction is usually encountered in the newly infected or actively diseased persons than in older or more stationary tuberculous processes. But inasmuch as a positive tuberculin reaction is conditioned by properties inherent in the skin which may present considerable individual variations, it is supposed that the thickness of the skin, its innervation and fullness of blood-vessels and capillaries, etc., may play an important rôle in the resultant tuberculin reaction.

No general agreement obtains that a close association exists between allergy and immunity in tuberculosis. Most investigators and especially in Scandinavia where the B. C. G. vaccination is widely practised, have followed the contention by Heimbeck (1) that «allergy is synonymous with immunity.» The wellknown investigations by Heimbeck have shown that pupil-nurses exposed to tuberculous infection, contract the disease in far greater proportions if they enter the service tuberculin-negative than tuberculin-positive, irrespective whether the allergic state is produced by spontaneous tuberculous infection or artificially with B. C. G. On the other hand, the contrary experience has been reported by the American investigators Harrington and Myers (2) and the Swedish investigator Herlitz (3) in serial studies on children. These workers have shown in an extensive material collected on school-children that tuberculinpositive individuals are excessively more susceptible than tuberculin negative individuals to contract tuberculous disease. Thus, they consider the allergic tissue much less tuberculo-resistant than the anergic tissue. In a large series of experimental studies, Birkhaug (4) has succeeded in dissociating the allergic component from the immune component by inoculating virulent tubercle bacilli into primarily infected experimental animals after having abolished the allergic state by continuous treatment with tuberculin. He finds that the immunized anergic animals remain far more tuberculo-resistant toward new virulent inoculation than corresponding groups of immunized allergic animals. This condition of anergy with retention or increase of tuberculo-resistance has been called by Birkhaug *ialthergic immunity*. He concludes that tuberculo-allergy is biologically different from tuberculo-immunity and that immunity in tuberculosis can be established without allergy. Although we may presuppose that the *modus operandi* of tuberculo-resistance runs parallel in man and the experimental animal, nevertheless, it should be pointed out that the massive parenteral inoculation of tubercle bacilli into the experimental animals employed by Birkhaug differs essentially from the aerogenic infection of man with very few tubercle bacilli. This may explain the fact that the acquired tuberculo-resistance in man is excessively more complete than that which obtains in the experimental animal.

It has been known for some time that a positive tuberculin

reaction may become weaker or even completely negative in a series of disease entities as well as in conditions of tuberculous etiology. This is especially true in most acute infections. In certain forms of tuberculous disease, such as miliary tuberculosis, meningitis or advanced pulmonary tuberculosis one finds that an erstwhile positive tuberculin reaction suddenly becomes negative. This occurs also in cachectic conditions produced by a series of disease entities. Now and then one may encounter a negative tuberculin reaction in tuberculosis in the serous membrances as in joint or bone tuberculosis. When the tuberculin reaction fails to become positive in cases massive tuberculosis, one attributes this fact to the tissue being supersaturated with tuberculin, or in other words to a process of desensitization similar to that produced by injections with tuberculin. Also in chronic inactive diseases supposed by many to be of tuberculous etiology, such as *lymphogranulomatosis benigna* (Boeck's sarcoid), the tuberculin reaction is mostly negative, only to become positive when the disease is eradicated. In older individuals who in earlier life have been exposed to tuberculous infection, one finds that the tuberculin reaction becomes weaker or completely negative. This has been accepted by many as an expression of a cured condition, biologically speaking. The same condition is also encountered in various endocrine disturbances. Thus, E. Coulaud (9) observed among women that the anergic phases paralleled different stages in their genital life and that therapy of the thyroid gland reduced while that of the ovaries increased the allergic hypersensitiveness. One finds also described cases of reduced or abolished allergy during under-nourishment as well as during excessive treatment with l-ascorbic acid [Birkhaug (5)]. When none of the aforementioned causes could explain the phenomenon, it was supposed that a familial tuberculin-anergic diathesis might be invoked inasmuch as several cases of negative tuberculin reactions were found to occur within the same family [M. Paretzky (6)].

Disregarding the above-mentioned conditions, it is now customary to exclude tuberculous infection when a Mantoux test with 1 mg tuberculin gives a negative reaction. Thus, the tuberculin reactions forms the basis for our entire diagnostic and epidemiological tuberculosis work.

It does not appear, however, that we indiscriminately can accept a negative tuberculin reaction as an indicator that tuber-

culous infection has not occurred. The American investigators Crimm and Short (7) have reported calcified foci in the lungs and bronchial glands in a series of tuberculin-negative persons in whom a tuberculous etiology was probable. Paretzky has shown a shift from positive to a negative tuberculin reaction in 59 cases (5.9 per cent) among 1,002 persons. In Sweden, O. Ljung (8) has reported a similar investigation concerning 543 tuberculin-positive school-children who during a follow-up investigation 1 to 8 years later showed a 6.8 per cent shift from positive to a negative tuberculin reaction with the Mantoux (1 mg.) test.

A series of sporadic observations have been published in America and France which show that a positive tuberculin reaction may turn negative in individuals with pulmonary tuberculosis in whom the disease was not so far advanced that this could explain the phenomenon, and in whom none of the afore-mentioned conditions was known to be present. In the available literature, the author has not seen described similar observations in this country. Publication of such a case, which the author has had the opportunity to observe during a long period, might be of interest.

A case of active tuberculosis with a negative tuberculin reaction.

The patient is a 23 year old man of a healthy family. No serious disease has occurred during his past history. The tuberculin test was not performed previous to admission at the sanatorium. In February 1940 a smaller haemoptysis occurred while he was in excellent health. Roentgen-examination of the lungs revealed nothing pathological. He was later in good health and in complete working condition until in January 1941 he suffered with moderate coughs and brought up small amounts of purulent sputum. This continued during the spring and he experienced no malaise until a new haemoptysis in May the same year brought him to a physician. Roentgen-examination at this time showed (Fig. 1): exsudative right-sided superior lobe lesion with cavity laterally in the right field. In the left apex and upper field a few peri-bronchially situated lightly saturated flecks suggestive of bronchial spread. At the admission at the sanatorium on June 8, 1941, his general condition was good although he was quite pale. He was afebrile and presented no dyspnoea. Sedimentation reaction was 25 mm. Tubercle bacilli were present in the direct smear. The blood presented the following figures: Hb., 88 percent (14.1 g); R. B. C., 5 millions. Colour index, 0.8; W. B. C., 4,843, of which Eosinophiles, 1.5 %; Basophiles, 0 %; Stabs, 4.5 %; Segments, 56 %; Lymphocytes, 27.5 % and Monocytes, 10.5 % (200 cells were counted). The roentgenogram of the lungs as described. Pirquet



Fig. 1.

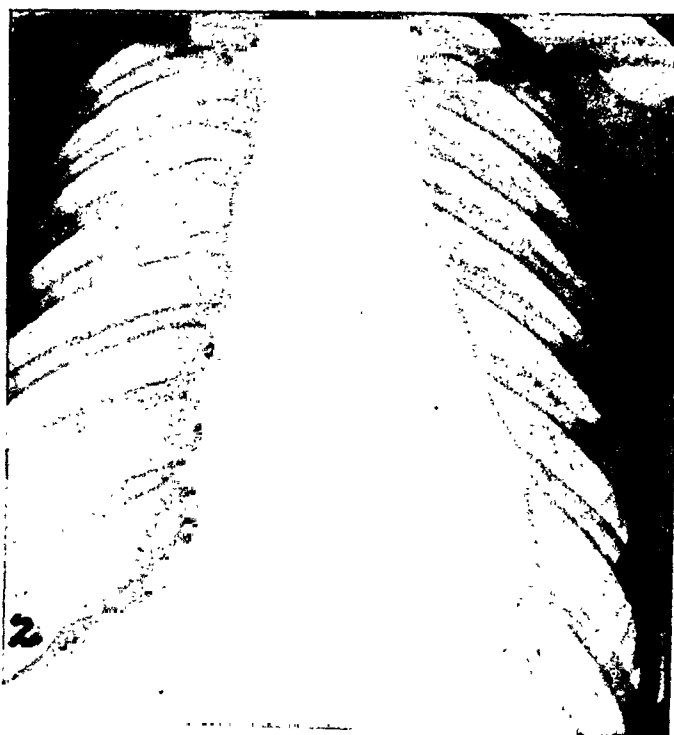


Fig. 2.

test, negative (0—0 mm) Mantoux test with 1.3 and 5 mg tuberculin, negative (0—0 mm) read 48 and 72 hours afterwards.

On July 3, 1941, right-sided pneumothorax was done and on August 8 and November 21 thorascopi and right-sided cautery. Several large adhesions laterally and upward were cut. Medially the lung was surface adherent to the mediastinum. No reaction to the cauterization.

During the continued pneumothorax treatments, the cavity was seen to disappear and during 4 months he has been abacillar. His general condition picked rapidly up and became very good. The sedimentation reaction fell from 25 mm to 3 mm after 4 months residence and has since continued low. During approximately half a year he has been on his feet and has taken the full open-air cure, without cough or expectoration. He has remained afebrile during the whole time.

Tuberculin tests have been done with 2 months interval since the admission and these have continuously been negative with doses up to 10 mg tuberculin (Mantoux). He was likewise negative when 3 mg tuberculin was injected subcutaneously. No occasion occurred to doubt the diagnosis of tuberculosis. But on account of the constant anergic condition, the expectorate was inoculated into guinea pigs which died of generalized tuberculosis.

The roentgenogram taken April 24, 1942 (Fig. 2) shows complete atelectasis in the right upper lobe without any visible cavity. No progression is observed in the process in the left side.

Epicrisis.

Young man with cavernous pulmonary tuberculosis, presented on admission at sanatorium good general condition, increased sedimentation reaction, light hypochromatous anaemia, normal blood picture, and was afebrile. During the entire stay at the sanatorium he has been tuberculin-negative with large doses of tuberculin. He was treated with collapse of the cavernous lung, the cavity was effectively closed and disappeared and he remained abacillar after approximately six months sojourn at the sanatorium. His general health became very good after a short while, he gained in weight continuously and the haematological status has on 3 occasions been found normal.

None of the afore-mentioned allergy-reducing conditions has been found in this case. The tuberculous condition, which has shown continuous improvement since admission, has not been in such a decided active phase that this can account for the constant anergic status. Against this hypothesis speaks also the excellent general condition, the afebrile course of the disease, the results

of the haematological examinations and first and last the disappearance of the cavity and expectorated tubercle bacilli.

In order to elucidate whether or not a familial tuberculin-anergic diathesis might explain the phenomenon, the author learned of Birkhaug that the patient's sister, who earlier was tuberculin-negative, was vaccinated with B. C. G. (Rosenthal's multiple puncture method) (10) and became strongly positive (Mantoux 1 mg) already 12 days after vaccination.

In view of the fact that the patient's condition became more favourable during the entire stay at the sanatorium, one is permitted to believe that his immunizing capability was in order. It is natural, therefore, to suppose that this case presents an excellent example of *ialthergic immunity*, in which tuberculin hypersensitivity is eliminated while immunity is retained. If the tuberculin-anergic condition were due to an organism super-saturated with tuberculin, and on this account was unable to react with a positive tuberculin test, one might expect that the allergic hypersensitivity would return gradually as improvement occurred in the diseased condition. We have already stressed that this has not been the case.

One might object to the repeated tuberculin tests being performed in these examinations on the ground that the patient in reality was artificially desensitized and that this might explain the anergic status. It should be recalled that these tuberculin tests were performed with two months intervals. It is known, however, that the desensitized state does not persist more than 7 to 12 days after the last injection of tuberculin (100 mg tuberculin is necessary for tuberculous guinea pig weighing ca. 400 g) at which time the animal responds promptly with a positive tuberculin reaction (Birkhaug). It would thus require far greater and more persistent doses of tuberculin than those employed by us to retain our patient in a tuberculinanergic state. It should also be emphasized that the tuberculin reaction was negative the very first time the test was done, on the admission to the sanatorium of our patient.

A method which possibly could be employed to ascertain the presence of tuberculo-immunity in our patient, is that suggested by Rolv Thorkildsen (11). This method is based on the Koch phenomenon and suggests the possibility that the focal reaction which one observes in the multiple B. C. G. punctures in the skin, may be iden-

tical with this phenomenon, and might thus serve to indicate the presence of acquired immunity.

The classical Koch phenomenon shows the following: when a noninfected guinea pig is inoculated with virulent tubercle bacilli, the site of inoculation presents no visible lesion before approximately 2 weeks later when the overlying skin necrotizes and a persistent sore is produced. On the other hand, when a tuberculous guinea pig is inoculated in the same manner, already *two days later* an infiltration forms at the site of reinoculation, the overlying skin becomes intensely inflamed, necrotizes, sloughs off and the process heals rapidly. The Koch phenomenon has also been employed as a proof that a tuberculous individual is in possession of a certain degree of immunity towards further tuberculous infection. We were anxious to observe how our tuberculin anergic patient would react with the multiple puncture B. C. G. vaccination.

On March 7, 1942, the above-mentioned patient was vaccinated with B. C. G. (Rosenthal's method). For control purposes, the author vaccinated at the same time and with the same vaccine a tuberculin-allergic individual as well as a normal tuberculin-nergic individual. Already two days later, the tuberculous tuberculin-nergic patient reacted with fully developed ca. 2 mm wide papules, presenting redness and infiltration in the respective vaccination punctures. The papules remained unchanged during approximately two weeks when they began to desquamate and gradually disappear. The tuberculin test (Mantoux 1 mg) was and remained persistently negative.

The tuberculin-allergic individual reacted more intensely in the same manner. Already two days after vaccination, approximately 3 mm wide, intensely red papules were observed which rapidly became confluent and produced an inflamed infiltrated area measuring ca. 30×50 mm. The papules pustulated in the centre, formed a dry crust which desquamated, leaving a lightly ochre-pigmented area without any ulceration.

The normal tuberculin-nergic individual reacted in an entirely different manner. No local changes occurred in the vaccination punctures before twelve days later. At this time we observed definite papules in 36 punctures. However, the papules were smaller and somewhat paler than those seen in the two other BCG-vaccinated persons. In the course of one month, the papules began to

desquamate and soon thereafter disappeared completely. The Pirquet tuberculin test became positive already 3 weeks after vaccination (6×5 mm).

Thus, we have observed the peculiar phenomenon that both infected individuals, i. e. the tuberculin-nergic tuberculous patient and the tuberculin-allergic person, reacted simultaneously in approximately the same manner, and that the focal papular-pustular changes occurred in the vaccination area already two days after vaccination, while in the non-infected tuberculin-nergic individual the focal papular reaction occurred first twelve days after vaccination. Now let us suppose that the accelerated focal papular reaction in the BCG-vaccination punctures really is identical with the Koch phenomenon, as Thorkildsen claims. Accordingly we might be permitted to suppose that the accelerated BCG-vaccination reaction described by us does represent an expression of acquired tuberculo-immunity which is possessed by infected persons, whether tuberculin allergic or nergic, and not by non-infected tuberculin nergic persons.

Thus, two things emerge from our observations, namely, that tuberculin allergy may disappear completely during active pulmonary tuberculosis which is improving, and that the interdependence of immunity on allergy is not as solid as many authors would have us believe. Our case of tuberculo-resistant tuberculin nergic recuperating phthisis represents, so-to-speak, the clinical picture of *iatergic immunity* which Birkhaug has demonstrated extensively in the desensitized tuberculous animal. But in a discussion of the interrelation of tuberculo-immunity and tuberculin-allergy too many unknown factors are involved which prohibit us from drawing any definite conclusion from one single observation.

Summary.

A repeatedly tuberculin negative tuberculous person reacted toward the cutaneous BCG-vaccination with accelerated focal papular lesions already two days after vaccination in a manner less violent than a tuberculin positive individual while a non-infected tuberculin negative person reacted with focal papular lesions first two weeks after the cutaneous BCG-vaccination. These findings suggest that tuberculo-immunity may exist in the complete absence of tuberculin allergy.

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Some investigations on the protective colloids in urines and their relationship to other physico-chemical properties of urines.

By

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(Submitted for publication August 7, 1942.)

For many decades it has been held that kidney stones were largely due to the colloidal properties of the urine. After these questions had been investigated around the turn of the century and in subsequent years, interest in the colloids of the urine began to lag as it was found that a number of other factors were involved, for example geographical conditions, heredity, race, diet, stasis, infection, metabolism disturbances, skeletal affections etc. But it was especially MEYER'S work on the degree of saturation of the various crystalloids in the urine which caused the colloids to fall into the background. Some authors have even claimed that the colloids of the urine are of no significance in the genesis of lithiasis.

There can be no doubt that urine is often a supersaturated solution, even though the saturation degree of the individual salts is not determined in relation to water but in relation to the total salt concentration. Thus Swift gives the following figures for oxalic acid and calcium oxalate:

0.565 calcium oxalate corresponds to 0.351 mg oxalic acid and this is soluble in 100 cm³ water. In other words 5.3 mg oxalic acid

in 1500 cm³, but the daily secretion is 15—20 mg. Normal urine therefore contains 3—4 times the maximum concentration and in pathological conditions with oxalic acid poisoning Umber has found that 68 times the maximum concentration was dissolved. The same holds true for uric acid.

Even though the various salts in the urine mutually hold each other in solution, the colloids must apparently have some significance. For example a urine may contain large quantities of oxalate and all of it is dissolved, while on the other hand a urine may contain little oxalate, all of which is precipitated, probably because of the colloids. This can also be demonstrated by dialysis. If a urine is dialysed with a large amount of water and the water is then carefully evaporated off, the crystalloids will be precipitated long before the original urine volume is obtained. This precipitate consists of calcium oxalate, calcium phosphate and uric acid. But it is not possible to produce urine artificially simply by mixing the various salts together. A mixture of this type will always precipitate.

Our knowledge of the urine colloids is very limited. The quantity depends on the diet. It is increased by a diet rich in proteins. There is also an increase during pneumonia and of the non-albuminous colloids in acute and chronic kidney conditions. The colloids found by dialysis are: mucin, nucleic acids, chondroitin sulphuric acids, glycogen and a complex N-containing carbohydrate. All the colloids are very stable and tolerate boiling. It is not known whether the urine colloids originate from the kidney cells or the serum.

There are several different ways in which the urine colloids may be studied. We found it most convenient to use Zsigmondy's gold count reaction, which provides a measure for the so-called protective colloids. The method is based on testing the protective capacity of urine against a red gold colloid which is precipitated with 10 % NaCl. Zsigmondy's original method for producing the red gold colloid is very complicated and requires a special laboratory free from disturbing dust and chemicals. He precipitated a gold chloride solution with formaldehyde. Simpler methods have since been evolved, much less sensitive, where precipitation is obtained with glycerose or other substances. We have used a method described by Borovskaya (*Z. Immunitäts.* 82, 178—182, 1934). She precipi-

tates with sodium citrate. In this manner it is easy to obtain a gold colloid with a cherry-red color and with properties which characterize the red gold colloids.

Some earlier investigations have been made with the gold count reaction, especially by Lichtwitz in 1909 and 1910, in which it was demonstrated that normal urine contains colloids which have a protective influence on the red gold colloids, that the urine colloids became more fine-particled and had a stronger protective capacity when heated, and that in some cases a direct proportionality could be demonstrated between the solubility of the uric acid and the quantity of the urines protective colloid. Since then investigations have been carried out by Ottenstein who showed that the protective colloids increased on a diet rich in meats, and by Ferguson who found higher values for the protective colloids in patients with kidney stones than in normal persons. Experiments on rats have been carried out by Hammarsten, who found no difference in the values in rats with or without stones.

However in the above mentioned investigations the crystalloid contents and other physico-chemical properties of the urines examined have not been taken into consideration, and in the comparative studies which have been made there has been no control of the diet of the experimental persons.

The object of this investigation has been to examine whether it was possible to demonstrate a difference in the amount of protective colloids in urines of patients with stones in the urinary tract compared with urines from healthy persons and patients with other affections. And finally whether an eventual demonstrable difference had any relation to other physico-chemical properties of the urine.

Urine samples were taken from patients and healthy persons, all of whom had held an approximately uniform diet as all had been living on the ordinary hospital fare for at least 24 hours before the samples were taken. Even though we have not used a standard diet, at least the variations have not been large.

Among the urolithiasis patients we have only examined those who had »primary», uncomplicated stones in the urinary tract. In all cases the investigations have been made only where the ordinary methods of examination (including mic roscopy) have revealed no pathological findings.

We have examined partly fresh morning urines, partly several samples taken during the day in order to detect any eventual day variations.

In addition to measurement of the colloid contents and the ordinary examinations for albumin, sugar, cylinders, red and white blood corpuscles, we have determined diuresis, specific weight (Hammerschlag's method), pH and refractometric measurements (to get an idea of the quantity of crystalloids).

For the pH determinations we have partly used Sørensen's method. Most of the determinations however are made with indicator paper (Lyphan). The refractometry was done with an Ein-tauch refractometer at 18–20°.

As a measure for the colloid content we have determined the smallest quantity of urine which, after having been mixed with 10 cm³ gold colloid for 3 minutes, was able to prevent coagulation for 5 minutes after the addition of 1 cm³ 10 % NaCl solution, and we have only used gold colloid which exhibits no change of color on the addition of 0.1 cm³ NaCl solution, but where 0.2 cm³ gave a violet and 0.3 cm³ a blue color.

As we shall see later, the colloid measurements are to a great extent carried out in dialysed urines. The dialysis has been performed in closed cellophane filters for 48 hours (24 hours proved several times to be insufficient). That dialysis was always complete was controlled by specific weight, pH, demonstration of absence of chloride and in several cases also refractometrically.

The very first preliminary investigations of the colloid content in fresh morning urines showed highly variable results with the colloidal gold reaction. It then seemed that the method was not applicable unless the sources of error which lay in the varying crystalloid quantity (i. e. chiefly NaCl) in the urines could be eliminated. On the other hand it was to be expected that a removal of the crystalloids and a leveling of the pH which would be the result of dialysis, would have an influence on the size and number of the colloid particles and thus on the result of the colloidal gold reaction. There would also be the additional source of error caused by the purely physical dilution as a result of dialysis.

In order to determine what influence changes in the pH would have on the result of the colloidal gold reactions, several portions of the same urine were mixed with acetic acid or potassium

hydroxide so that reasonable variations in the pH were obtained (varying from 3.9 to 6.5) in the different samples. It was then found that regardless of any changes in the pH, and regardless of whether the change was made before or after dialysis, the colloidal gold reaction gave the same values with the exception of insignificant differences in the coloring.

The volume of the dialysate varied after the completion of dialysis, depending on the original concentration of the urine. The volume was usually increased by about 10—25 % with limits at 5 % and 40 %. In order to determine the influence of this dilution, we have in some cases performed the colloidal gold reaction both directly in the dialysate and after the latter was still further diluted to a total dilution of 50 %. There were no large differences between the two samples from the same dialysate, only an insignificant transition for example from red-violet to violet-red or red to red-violet, rarely so much as from red all the way to violet.

Thus we have not been able to demonstrate any significant difference in the result of the reaction after changes in the pH and after a reasonable dilution. In addition as the object of this investigation was a comparison of the colloid content of various urines rather than an exact measurement of these contents, we have disregarded these sources of error. In the samples discussed below we have therefore measured specific weight, pH and the refractometric value before dialysis, and carried out the colloidal gold reactions after dialysis without making correction for the dilution which has taken place.

Material.

The preliminary experiments which were made to test the technique and which were made with urines taken at any time during the day, showed that there were considerable variations in the results of the colloidal gold reaction.

Experiments were therefore made with fresh morning urines, 53 times in all, of which 25 were from patients with urolithiasis and 28 partly from healthy persons, partly from patients suffering from other affections (of which 1 with adenoma prostatae and 1 with hypernephroma renis). The results of these tests are presented in Table I, where we have divided them into groups according to the

Table I.

The necessary amount of urine in cm³.

	Group I ≤ 0.5	Group II 0.6—1.0	Group III > 1.0
Diagnosis:			
Urolithiasis	16	5	4
Other affections (not «stone-formers»)	22	3	3

amount of urine which was necessary to prevent precipitation of the gold colloid.

As it appears, there is no pronounced difference in the values from stone patients and non-stone-formers. In Group III, i. e. those with the relatively lowest colloid content in the urine, there are 4 patients with primary stones and 3 others. One of these was a healthy person, the other was hospitalized under the diagnosis Ob-stipatio, Epilepsia, while the third suffered from ulcer per. duod. c. absc. subfren. et empyemae pleurae. The 3 non-stone-formers in Group II had the diagnoses Cystis dermoid. sacral., Adenoma prostatae and Paralysis generalis.

As these investigations did not seem to afford any basis for variations in the urines content of colloids in stone-formers as compared to non-stone-formers, an investigation was made of day variations in 33 individuals, of which 21 had urolithiasis. In this experiment from 5 to 9 samples were taken from each patient, distributed as far as possible throughout the day. The result of this investigation appears in Table II, where there is also a division into groups according to the size of the variation in the quantity of urine which was necessary to prevent precipitation of the gold colloid.

Table II.

Day variations expressed in cm³ urine.

	Group I ≤ 0.5	Group II 0.6—1.0	Group III > 1.0
Diagnosis:			
Urolithiasis	9	3	9
Other affections (not stone-formers).....	10	1	1

The one patient recorded in Group III under non-stone-formers, was hospitalized for pleurisy and had a couple of attacks of pains which were very suspicious of urolithiasis, but roentgenologically (with and without contrast) no definite evidence was obtained for such a diagnosis.

With the exception of the possibility that this patient may have had a stone, we find here, in contrast to the investigation of morning urines, a striking number of urolithiasis patients in Group III, i. e. in the group which in the course of the day showed the greatest variations in the urines' content of colloids. In other words: *The urines from stone patients examined by us showed much greater variation in colloid concentration during the course of the day than urines from non-stone-formers.*

If we regard the gold colloidal values obtained as a rough measure of the urines' protective capacity, and compare these values with the values found for other physical properties of the urine, especially its crystalloid content, recorded by the refractometric value before dialysis, we will find a pronounced parallelism in most cases. This is seen in Curves 1 and 2 on Figure 1. Thus when the colloidal gold value is high, the refractometric value is also relatively high. It is especially interesting that the curves for specific weight, refractometric value and gold colloid value follow each other approximately also in urolithiasis patients who showed the extreme variations in colloid content in the course of a day (Curve 2).

The large day variations for 3 of the 9 stone patients is most likely due to abundant drinking with high diuresis, as this has been from about 3000—3200 cm³ in these 3 patients. The diuresis of the others in this group lies with one exception (690 cm³) much higher than in the other groups, with an average of 1575 cm³ (variations from 690 to 2175 cm³) while in Group II the average is 1175 variations from 625—1480 cm³) and in Group I the average is 860 cm³ (variations from 630 to 1400 cm³).

It might therefore appear that the variable colloid content was simply an expression of the dilution of the urine and this is probable in many cases. But on the other hand there are, as shown in Figure 1 (Curve 3), urines which show the same high colloid content throughout the day, while at the same time the specific weight varied from 1006 to 1012 and the refractometric value from 15.0 to 23.0. Curve 4 shows the reverse, namely how in some cases the

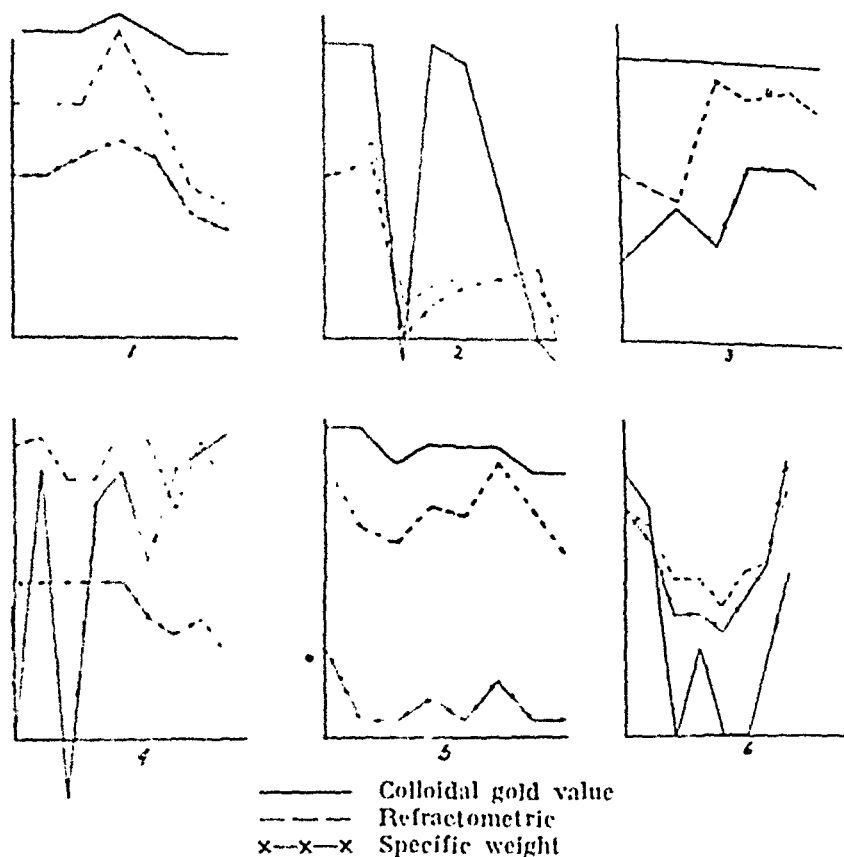


Fig. 1.

specific weight is the same while the colloidal gold value shows great variations, which are sometimes completely independent of the variations in the refractometric values. This shows that although the majority of the material exhibits a parallelism between the various values, *there are several cases where there are considerable day variations without corresponding variations in the other values.* We have not been able to find any satisfactory explanation for this phenomenon. It is impossible for the present to ascribe it any significance with relation to urolithiasis formation.

Our investigations have thus shown that under approximately the same conditions there may be considerably large variations in the relative colloid content of the urine. In our present material the greatest variations are found in patients who have or have had urolithiasis.

We have hitherto been unable to carry out our investigations under ideal conditions, as we have not been able to keep our patients

on a standard diet with uniform quantities of liquid. We have therefore under the present conditions not had the opportunity of examining the significance of for example a diet rich in meat over a long period as compared with a largely vegetable diet. Nor have we had the opportunity of following the patients over a long period. We have at most been able to control them for a few days. As appears from Curves 4, 5 and 6 there have been considerable variations from day to day. It would also have been advantageous if we had the opportunity to carry out systematic bacteriological examinations of all the urines, with regard to an eventual minimal bacteriurea. We do not know what influence various medicaments may have on the disperse phases, but some of our patients were given a little papaverin and, or small quantities of morphine during the experimental period.

It is possible that investigations carried out under more ideal conditions might reveal constant or periodical disrelations between the quantity of colloids and the quantity of crystalloids, and these latter might be of significance for the genesis of urolithiasis.

In conclusion we would like to extend our thanks to Magister J. Bøe, Professor Johs. Lindeman and Dr. Ketil Motzfeldt for advice and help during the course of our work.

Summary.

In preliminary investigations the authors find that during the day, urines from stone-formers probably show greater variations in the relative colloidal protective values (colloidal gold method) than those from non-stone-formers. The authors also show that these variations are not always parallel to coincident variations in the values of crystalloids (refractometric method).

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From the Blegdams Hospital, Copenhagen (Director: Professor H. C. A. Lassen, M.D.).

A Clinical Study of Erysipelas with Special Reference to Primary Foci of Infection and Differential-Diagnostic Difficulties.

By

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(Submitted for publication August 20, 1942.)

The scope of the present work was to find out what affections and regions most frequently are the primary foci of infection of erysipelas, and to illustrate the differential-diagnostic difficulties met with in this affection.

The material comprises two groups of patients:

1) 715 patients who during the years 1936—40 stayed in Blegdams Hospital under the diagnosis erysipelas.

2) 132 patients who during the years 1936—40 were admitted to Blegdams Hospital under the diagnosis erysipelas but who actually suffered from other diseases.

The distribution of the 715 erysipelas patients according to the respective months of admission appears from the histogram (Fig. 1).

From Fig. 1 it is evident that the majority of erysipelas cases occurs in the winter months, an absolute minimum being found in the summer months. This agrees with Birkhaug's (4) and Hegler's (8) reports. Keefer and Spink (12) examined the seasonal

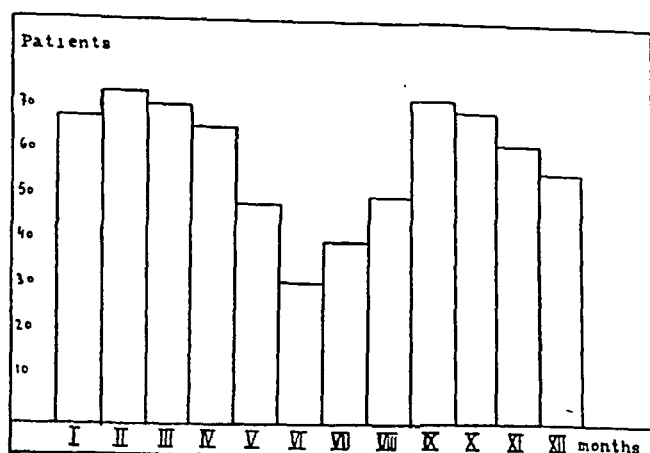


Fig. 1. The distribution of 715 erysipelas patients after the months of admission.

variations for different hemolytic streptococcus infections, among which were 1400 cases of erysipelas. They found an accumulation of cases during the winter and early spring months.

The distribution of age among the 715 erysipelas patients is shown in Table 1.

Table 1.

Age (years)	Patients	per cent	Age (years)	Patients	per cent
50—10	56	7.8	50—60	166	23.2
10—20	26	3.6	60—70	117	16.4
20—30	75	10.5	70—80	56	7.8
30—40	102	14.3	above 80	7	1.0
40—50	110	15.4			

From Table 1 it is evident that the majority of cases of erysipelas occurred in the age-class 50—60 years. This is not quite in accord with Birkhaug's (4) and Hoyne's (10) reports. These authors find the greatest number of erysipelas cases at the age of about 40; Hoyne's material comprises 1193 cases. Schultz (17) finds the greatest number of erysipelas cases at the age of 46—50 years, whereas Keefer and Spink (12) on the ground of 1400 cases find a maximum between 40 and 60 years of age.

Only 7.8 per cent of the erysipelas cases were found in children

below 10 years of age, the first 3 years of life being those in which children are specially prone to be attacked. The distribution appears from Table 2.

Table 2.

Age (years)	Patients	Age (years)	Patients
0—1	8	5—6	3
1—2	12	6—7	4
2—3	13	7—8	3
3—4	7	8—9	1
4—5	5	9—10	0

Among the 715 patients of the material were 494 women (69.1 per cent) and 221 men (30.9 per cent). This conflicts with the majority of reports concerning the sex distribution in erysipelas. Thus Birkhaug (4) reports 60 per cent of men and 40 per cent of women, and Lehmann (13) on the ground of 2340 cases of erysipelas finds 56 per cent of men and 44 per cent of women. These authors try to explain the preponderance of men by their being more exposed to various traumata and to bad weather during the winter months. However, Aaser (1) in a hospital material of patients finds 73.5 per cent of women with facial erysipelas against 26.5 per cent of men.

In the present material was found a very considerable female preponderance. This is in part due to the fact that the material comprises a relatively great number of cases of erysipelas on the lower extremities (37.5 per cent), whereas most other materials only comprise about 10 per cent, and the great majority of such cases occur in women (ulcus cruris). As is seen in Table 3, however, this does not explain the great female preponderance, which is likewise found in other localizations of erysipelas.

Migrant erysipelas was found in 5 cases, all of which occurred in 1936, prior to the introduction of chemotherapy.

Also with regard to the localization of the affection does the present material differ from the usual reports. Hegler (8) reports that erysipelas occurring on face and scalp amounts to 90 per cent of all the cases. Birkhaug (4) finds more than 90 per cent and Hoyne (10), 86 per cent of cases of erysipelas localized to the head.

Table 3.

The distribution of the erysipelas cases according to localization and sex.

Part of body	Number of cases	per cent	Men	Women	Women %
Head	411	56.8	150	261	63.5
Trunk	14	1.9	5	9	
Upper extrem.....	28	3.8	13	15	
Lower extrem. ..	273	37.5	55	218	79.9
	Total 726 ¹	100.0	223 ¹	503 ¹	

¹ In 11 of the patients the erysipelas was found to be localized synchronously to two of the mentioned parts of body, i.e. trunk + upper extremity in 4 cases, trunk + lower extremity in 1 case, head and trunk in 1 case, upper and lower extremity in 3 cases, and both lower extremities in 2 cases.

The present material thus differs fairly decisively from previous great erysipelas materials without it being possible to explain why.

The material can by no means be said to have been selected in any direction, Blegdams Hospital being that hospital to which are admitted virtually all the hospitalized erysipelas patients from the Copenhagen municipality. A comparison between this material and the numbers of erysipelas cases reported to the Copenhagen town-physician shows that far more than half of all the erysipelas patients in Copenhagen are admitted to Blegdams Hospital (quite apart from the eventual fallacious diagnoses among the reported but non-admitted cases).

Primary foci of infection of erysipelas.

It has been ascertained long ago that erysipelas is a streptococcal infection but the different authors still disagree considerably with regard to the portal of entrance of the bacteria or the primary foci of infection of the affection.

Formerly an idiopathic and a traumatic form of erysipelas were distinguished between, the latter comprising those cases, where the trauma through which the bacteria had entered could be detected.

It is natural to assume, however, that when there is a question of erysipelas on an extremity or the trunk, all cases are «traumatic», even though the lesion in some cases is so small that it is overlooked. The majority of authors therefore share this assumption,

reporting as primary foci of infection accidental small wounds, operation wounds, scratching-wounds sustained in various skin affections, impetiginous wounds, burns, *ulcera cruris*, fissures due to dermatomycosis, etc. As further primary foci of infection of erysipelas occurring on the trunk and extremities of children are mentioned the umbilical region, circumcision, places of vaccination [Bauer (3)]

In many cases of facial erysipelas special conditions certainly assert themselves.

Hegler (8) mentions small wounds, scratches, insect-bites etc. as being the most frequent portals of entrance in cases of facial erysipelas, although he emphasizes too, that ear and nose affections not infrequently are primary foci of infection. Birkhaug (4) stresses the undoubtedly great importance of «nose-picking» and «ear-cleaning» for the occurrence of facial erysipelas, thinking, however, that erysipelas very seldom occurs on the mucous membranes. Hoyne (10) in 60 per cent of the cases of facial erysipelas was able to detect a lesion of the skin or of the mucosa. Roger (16) among 2411 cases of erysipelas found only 20 in which the pharynx was involved. Segall (18) has reported some cases in which an erysipelas of the nasopharyngeal mucosa had spread via the middle ear to the skin. Keefer and Spink (12) mention the possible importance of antecedent catarrhalia for the erysipelas, and that was emphasized notably by Anderson (2) who stresses particularly that the erysipelatous infection often is preceded by infection of the upper air-passages: Tonsillitis, pharyngitis and rhinitis may exist during a period of up to 10 days before the erysipelatous eruption appears. Holmes (9) draws attention to the great frequency of latent streptococcal infections in the nose and its accessory sinuses, and places this in relation to the frequent occurrence of facial erysipelas which, in his opinion, mostly originates from the nose. Schultz (17) opines that facial erysipelas cannot be considered a wound affection, because a wound is but rarely detectable, whereas a «catarrhal causation» often is found. Frequently there is a connection with the occurrence of angina which the author considers as a synchronously arisen coordinate symptom of the affection. Besides by Holmes (9) the nasal mucosa is reported to be the most frequent primary focus of erysipelas infection by Bauer (3), Rasch (15), Ustvedt (22), and others.

From this review of the literature it is evident that there is fairly much disagreement with regard to the primary foci of infection of facial erysipelas. Several authors think that the trauma, in the widest sense of the word, plays the greatest part, whilst others are of opinion that mucosal affections and catarrhal diseases are the chief causes of the occurrence of facial erysipelas.

The author's own investigations.

As was mentioned before, the scope of the present work was to obtain a notion of the different primary foci of infection of erysipelas on the face as well as on the trunk and extremities, the material comprising 726 erysipelatosus affections in 715 patients.

As *sure primary foci of infection* are indicated wounds, fissures, eczemas etc., when the patient positively reports that the redness has appeared during such affections the existence of which moreover has been detected.

As *probable primary foci of infection* are indicated similar affections, when the patient is not sure of the affection having originated there, or when it has been impossible, after his admission, to detect the existence of the affection mentioned by him.

In all other cases the primary focus of infections is termed *uncertain*.

Table 4 illustrates the incidence of sure, probable and uncertain primary foci of infection of differently localized erysipelas.

Table 4.

Distribution of sure, probable and uncertain primary foci of infection in different localizations of erysipelas.

Localization	Number of cases	Primary focus of infection					
		sure		probable		uncertain	
		num- ber	per- cent	num- ber	per- cent	num- ber	per- cent
Erysipelas on face and scalp	411	151	37.5	83	20.2	177	42.3
„ „ the trunk	14	8	57.2	2	14.3	4	28.6
„ „ upper extremity	28	16	57.2	2	7.1	10	35.7
„ „ lower extremity	273	161	59.0	33	12.1	79	28.9
Total	726	336	46.0	120	16.7	270	37.3

From Table 4 it is evident that a primary focus of infection (sure or probable) of erysipelas is found much oftener in case of erysipelas on the lower extremities than in case of facial erysipelas. Thus a sure or probable primary focus of infection was detected in 57.7 per cent ($37.5 + 20.2$) of the cases of facial erysipelas, whereas the corresponding number of cases of erysipelas on the lower extremities was 71.1 per cent ($59.0 + 12.1$). The number of cases of erysipelas localized to the upper extremities and trunk is too small to permit of comparing it with the other two groups, but apparently the ratio is the same with regard to the incidence of erysipelas with known primary focus of infection as that of erysipelas on the lower extremities, as might be anticipated.

These conditions are highly in favour of other than »traumatic» causes playing an essential part as primary foci for the infection with facial erysipelas.

Table 5 is a more detailed survey of the different sure and probable primary foci of erysipelas on face and scalp.

It is seen that a sure or probable primary focus of infection in relation to the nose and ears was detected in the great majority of the cases, whereas other facial regions and the scalp presented such foci far more rarely.

Moreover it is seen that the erysipelas affection in no small number of cases occurred in sequel to various mucosa affections (otitis media, rhinitis, rhinopharyngitis, sinusitis, conjunctivitis, dacrocystitis), namely, $20 + 13$ cases altogether. These cases certainly cannot be considered to be of »traumatic» origin, and on drawing a parallel between the cases of »traumatic» and »non-traumatic» origin, they must be deduced from the sure and probable cases reported for facial erysipelas. Thus there remain 134 cases of facial erysipelas of reliably »traumatic» and 70 cases of probably »traumatic» origin, i.e. altogether 49.6 per cent of all the cases of facial erysipelas (32.6 per cent $+ 17.0$ per cent).

On comparing this with the number of sure (161) and probable (33) primary foci of infection in cases of erysipelas on the lower extremities which may all be considered to be »traumatic» (cf. Table 8), and which amount to 71.1 per cent of all the cases of erysipelas on the lower extremities, it is seen that »traumatic» play

Table 5.

Sure and probable primary foci of facial erysipelas.

Primary focus of infection	Number of cases	
	sure	probable
The nose		
»Wound in the nose» (eczema vest. nasi). — Rhinitis sicca ant. — Atrophic rhinitis	49	30
Wound outside on the nose	9	5
Wound on the root of the nose (spectacle wound)	2	2
Nasal furuncle	5	0
Chronic rhinopharyngitis and purulent rhinitis	0	3
Chronic maxillary sinusitis	0	1
After galvanocauterization for epistaxis	0	1
Gummatous ulcer of the nose	0	1
Pat. asserted positively that it had originated from the nose, a sure primary focus not being detectable however	0	9
Total of nasal primary foci of infection	65	52
Other facial regions		
Facial impetigo	3	0
Facial pityriasis	0	1
Facial eczema	2	1
Facial contusion wound. Facial incision wound.		
Excoriation	5	1
Facial furuncle	3	1
Nuchal furuncle	2	0
Insect-bite in the face	2	0
Strophulus	0	2
Parulis	0	2
Facial zoster	0	1
Naevus papillomatosus	1	0
Operation for atheroma	1	0
Fissure at the corner of the mouth	1	2
Dacrocystitis	0	1
Purulent conjunctivitis	0	1
Total of other facial primary foci of inf.	20	13
The ears		
Otitis ext. — Eczema auris. — Eczema retroauricularis.		
— Fissura auris ext.	33	2
Otitis media + otitis externa	13	3
Otitis med. supp. (acute and chronic)	7	4
Contusion wound and small excoriations on the ear ..	6	1
After incision in the ear (for hemoglobin determination)	1	0
Total of aural primary foci of infection	60	10

Primary focus of infection	Number of cases	
	sure	probable
The scalp		
Pityriasis capitis	4	1
Small wounds on the scalp (scratching).....	2	3
Pediculosis capitis	0	3
Psoriasis capitis	1	1
Contusion wound	1	0
Impetigo capitis	1	0
Total of primary foci on the scalp	9	8

a much more important part for their occurrence than for the occurrence of facial erysipelas.

It is therefore natural to assume that, even though the primary focus of infection of but 33 cases of facial erysipelas (8.0 per cent) was found to be a mucosa affection in the upper air-passages, the ears or the eyes, this mode of origin certainly is far more frequent. This is also suggested by the detection, in 77 of all the (715) erysipelas patients (10.8 per cent), of throat affections varying between slight redness and true angina with considerable redness and swelling, and in isolated cases even with furrings. Among those 77 patients were 58 with facial erysipelas, the erysipelas of the remaining 19 being localized to other places, and pronounced throat symptoms were only observed in the former.

Among the anamnestic data of 86 patients were moreover noted catarrhalia or «influenza» before or at the inception of the erysipelatous affection.

In some cases the synchronous occurrence of throat affection and erysipelas may be a mere fortuity, particularly in those cases where the latter was localized to other places than the face. In this connection it should, however, be mentioned that a patient with a throat affection due to hemolytic streptococci may happen, by first putting his fingers into his mouth or sucking them and afterwards scratching himself in some skin region or other, to perform an auto-inoculation of streptococci, which eventually may entail an erysipelatous affection.

From Table 6 it is evident that the most frequent primary focus of erysipelas on the trunk is mamma, particularly cancer mammae (ulcerated or operation cicatrix).

Table 6.

Sure and probable primary foci of infection of erysipelas trunci.

Primary focus of infection.	Number of cases	
	sure	probable
Cancer mammae	2	0
Operatio canc. mammae seq.	2	1
Intertrigo mammae	1	1
Hidrosadenitis axil.	2	0
Circumcision	1	0
Altogether	8	2

Table 7.

Sure and probable primary foci of infection of erysipelas on upper extremities.

Primary focus of infection	Number of cases	
	sure	probable
Contusion wound. Incision wound. Excoriation on the hand	3	1
Contusion wound. Excoriation on the forearm.....	5	0
Burn on the hand	2	0
Pustules on back of the hand	1	0
Digital fissure	0	1
Impetigo on upper extremity	2	0
Erysipelas on upper extremity with known primary focus of infection on the trunk.....	3	0
Altogether	16	2

Table 7 shows that accidental wounds and excoriations most frequently are the primary foci of erysipelas on the upper extremities.

From Table 8 it is evident that by far the most frequent primary affection in case of erysipelas on the lower extremities is crural ulcer or eczema; next follow accidental wounds and excoriations and, finally, various itching skin affections such as impetigo, strophulus and the like.

On examining Table 6, 7 and 8 it is evident that the primary foci of infection detected in virtually all the cases of erysipelas on the trunk and upper and lower extremities are »traumatic», that is to say, either really traumatic (accidental wounds of various

Table 8.

Sure and probable primary foci of infection of erysipelas on lower extremities.

Primary focus of infection	Number of cases	
	sure	probable
Panaritium on the toe	3	1
Wound infection on toe	5	1
Hyperkeratosis of toe	0	1
Epidermophytia	4	2
Interdigital fissure	3	0
Contusion wound and excoriation on foot	4	4
Fissure in calcaneal hyperkeratosis	1	1
Fissure in calcaneal psoriasis	1	0
Foot eczema	1	0
Foot ulcer	1	0
Crural ulcer	59	0
Crural eczema	26	4
Injectio in varices seq.	1	0
Crural wound infection	4	0
Wound infection on the foot	10	4
Crural contusion wound and excoriations	10	11
Crural burn	2	0
Contusion wound on the knee	2	0
Puncture wound on the knee	1	0
Scar on lower extremity	1	1
Insect-bite on lower extremity	5	0
Strophulus on lower extremity	2	0
Impetigo on lower extremity	12	0
Dermatitis herpetiformis	0	1
Bursitis prepatellaris.....	1	0
Psoriasis on lower extremity	0	1
Varicellae	0	1
Furuncle on femur.....	1	0
Erysipelas on lower extremity with known primary focus on the trunk (circumcision)	1	0
Altogether	161	33

kinds, excoriations, scratches, operation wounds etc.) or else so that the existing skin affections have given rise to solutions of continuity through which the bacteria have been able to enter.

Thus the result of the investigations in the primary foci of this erysipelas material is:

1) A sure or probable primary focus of infection of erysipelas on trunk and upper and lower extremities is detectable far more frequently than that of facial erysipelas.

2) All the primary foci of infection detected in the cases of erysipelas on trunk and upper and lower extremities are «traumatic» in the wider sense of the word. It is therefore natural to assume that the mode of origin has been traumatic also in those cases where a primary focus of infection was not detectable. The trauma has either been so small that it has escaped notice, or it has been healed when the patient was admitted to hospital.

3) In case of facial erysipelas the «traumatic» primary focus of infection likewise plays an important part (detected in 49.6 per cent of all the cases). In 8 per cent of the cases was detected a mucosa affection as sure or probable primary focus of the infection, whereas no primary focus of infection was detected in the remaining 42.3 per cent of the cases; however, a good many of these patients had had a catarrhal affection at the onset or shortly before the appearance of the erysipelatosus affection, or they presented a faucial affection on admission to hospital. Thus there seems to be no doubt that facial erysipelas frequently (perhaps in 30 per cent of the cases) arises secondarily, in sequel to an infection in the upper air-passages, the accessory sinuses, the ears or eyes.

The Differential Diagnosis of Erysipelas.

Diagnostication of a pronounced case of erysipelas generally is not difficult: The patient suddenly incurs a highly febrile affection with cold shiver, vomitings, delirations, and general exhaustion. At the same time some region of the skin or other presents a frequently shining redness and swelling, which is sharply delimited by an elevated, toruloid border. The patient has a sensation of tension in the affected region, increasing to real pain. Without treatment the affection spreads, often tongue-shaped, while the central parts become pale. On the affected skin regions both vesicles and bullae may appear, and desquamation ensues during gradual improvement.

However, far from all cases of erysipelas have such a «classical» course with such pronounced subjective and objective symptoms, and here is one of the causes of the differential-diagnostic difficulties. For the purpose of detecting the incidence of subjective and objective symptoms met with in erysipelas the material of erysipelas patients of the Blegdams Hospital during the 5 years from 1936 to 1940 (both years included) comprising 715 individuals was examined.

The frequency of the different symptoms appears from Table 9.

Table 9.

Erysipelas

The frequency of the commonest subjective and objective symptoms. 715 cases.

Subjective and objective symptoms	Number of cases	per cent
Rise of temperature to above 38°	656	91.8
Cold shiver	173	24.2
Vomiting-fits	133	18.6
Redness	715	100.0
Swelling	715	100.0
Sharp definition ¹	376	52.3
Elevated toruloid border ¹	92	12.9
«Islets» outside the chief affection	55	7.7
Bullae	145	21.0
Vesicles	36	5.0
Angina of various degrees	77	10.8

¹ Moreover, 77 patients had «typical erysipelas» (10.8 per cent) without the case-books containing any details concerning delimitation.

Thus it is seen that all the patients presented redness and swelling as a constant symptom, and even in a highly varying degree. On the ground of this material of patients the majority of whom were treated with chemotherapeutics, it is difficult to say anything about the extension of the affection at the borders as well as about the central clearing up.

As far as information was available 8.2 per cent of the patients had had no rises of temperature above 38° either at home or at the hospital. A good many of them were elderly persons or patients who had previously had one or several attacks of erysipelas, not-

ably on the lower extremities. In Jochmann's material (11) the cases free from fever amount to 7.4 per cent, whereas Erdmann (7), Tilesen (20) and Birkhaug (4) report a much lower percentage (1—2 per cent).

The sharp delimitation of the affection was only observed in a little more than half of the cases, which is, perhaps, partially due to this symptom persisting only as long as the affection is progressing; and it must be borne in mind that, in a great number of the patients admitted to hospital, the affection has culminated already before their admission.

The figures recorded in Table 9 for the different subjective symptoms must probably be considered to be too low, as it is not excluded that the symptoms were omitted among the data noted in the case-book, because the patients were not questioned about them.

As a rule the appearance of general and local symptoms is synchronous [Hegler (8), Norby (14)] but they sometimes occur at a couple of days' interval [Birkhaug (4)], and the present material even comprises 2 patients who presented them at 4 and 5 days' intervals, respectively. Naturally that may render correct diagnosis of the affection difficult during the first days, and it actually does happen that patients with erysipelas are admitted to hospital under diagnoses such as *febrilia*, *influenza*, *pneumonia*, *sepsis* etc.

Fallacious diagnosis may, of course, also be due to deficient examination, the physician f. ex. overlooking an erysipelas on the lower extremities, because the patient owing to the slightness or even absence of local symptoms does not draw attention to the affection or is not even aware of it.

10.8 per cent of the 715 patients examined suffered from more or less pronounced angina with conditions varying between moderate faucial swelling and redness and true tonsillitis with furrings.

Therefore it is not to be wondered at that many erysipelas patients are admitted under diagnoses such as for example *angina*, *mononucleosis* and *diphtheria*, for in certain cases the throat affection quite dominates the picture, whereas the local skin symptoms either have not appeared yet or are so insignificant as to be overlooked.

Among the 715 patients with erysipelas were 20 (i. e. 2.8 per cent) who were admitted under some other diagnosis.

The distribution of these fallacious diagnoses is recorded in Table 10.

Table 10.

Erysipelas patients admitted under fallacious diagnoses (20 cases)

Admission diagnosis	Number of cases
Febrilia (2), influenza (1), pneumonia (3), sepsis (1), rheumatic fever (1)	8
Observation for diphtheria (2), angina (2), mononucleosis (1)	5
Phlegmon (1), lymphangitis (1)	2
Observation for osteomyelitis	1
Acute otitis media, observation for mastoiditis	1
Purulent dacrocystitis	1
Buccal impetigo, epidemic parotitis	1
Exanthema	1

Much oftener does it happen, however, that various other diseases are mistaken for erysipelas.

During the period 1936—40, 827 patients were thus admitted to Blegdams Hospital under the diagnosis erysipelas; 695 of them had erysipelas, whereas 132 suffered from various other affections, which the referring physicians had mistaken for erysipelas.

In the Tables 11 and 12 are recorded the diagnoses made in these 132 cases.

Now the objection may be raised that the great number of fallacious diagnoses partially is due to the referring physician's press of business and, perhaps, ignorance of the clinic of erysipelas, but on reviewing the case-reports it is evident that also the hospital physicians who come across fresh erysipelas cases virtually every day have had difficulties of diagnosing the affection, and often disagreed in that respect.

Simple *capillary lymphangitis* may bear great resemblance to incipient erysipelas but the sharp toruloid delimitation is absent in lymphangitis, where the redness as a rule is not so homogeneous but more reticular, vanishing in the surroundings.

Truncal lymphangitis with the tender, firm cords, in whose surroundings the redness is found, should be easy to discern from erysipelas, so much more as it presents the tender regional glands. These may, however, be tender and swollen in erysipelas too, but that is rare.

The differential diagnosis between erysipelas and *phlegmon* is much more difficult, particularly in regions where the skin is thin, and because erysipelas may be conjoined or complicated with a phlegmon. However, in case of erysipelas the maximal redness, swelling and tenderness is in the periphery of the affection, whereas phlegmon presents the strongest reaction in the center. In case of phlegmon the boundary-line between sound skin and affection is somewhat indistinct, and the redness, besides being less shining than in erysipelas, is of a darker hue.

Also *abscesses*, *furuncles* and *carbuncles* may occasionally be difficult to discern from erysipelas but here, too, it holds still more than in the above-mentioned affections that the strongest redness, swelling and tenderness are seated centrally, and that the sharp, toruloid delimitation is missing. The existence of fluctuation will, of course, immediately afford the diagnosis.

Crural ulcer and contusion wounds with inflammation in the surroundings as a rule do not cause any rise of temperature, the general condition is quite unaffected, and typical local erysipelas symptoms fail to appear.

Varix inflammation and phlebitis present redness, swelling and tenderness following the vein cord upward on the extremity or in the surroundings of the infiltrated node, even though the redness may extend rather far outward in the surroundings. Palpation of the firm vein cord will afford the diagnosis.

As regards the other diagnoses recorded in Table 11 there is scarcely a question of differential-diagnostic difficulties after careful examination, apart, perhaps, from *phlegmonous dacrocystitis* which, in the case here observed, bore a striking resemblance to facial erysipelas, although the strongest reaction was found corresponding to the inner canthus.

Table 12 shows that, among the skin affections, *artificial dermatitis* and *eczema* are those which are most frequently mistaken for erysipelas. This is not to be wondered at, since a quite acute dermatitis or eczema, or exacerbations of such most frequently

Table 11.

Patients with admission diagnosis *erysipelas* (1).

Diagnosis made in the department	Number of cases
Abscess	11
Furuncle	3
Carbuncle	2
Lymphangitis	14
Phlegmon	11
Crural ulcer with inflammation	3
Varix inflammation	4
Phlebitis on lower extremity	3
Contusion wound with inflammation	3
Suppurative infrapatellar bursitis	1
Talocrural arthritis	1
Pyarthrosis of the humeral joint	1
Phlegmonous dacrocystitis	1
Parulis	1
Maxillary sinusitis	1
Osteomyelitis seq.	1
Acute mastoiditis	1

Table 12.

Patients with admission diagnosis *erysipelas* (2).

Diagnosis made in the department	Number of cases
Artificial dermatitis	26
Eczema	6
Urticaria	2
Erythema solaris	2
Pityriasis simplex	1
Facial streptodermia	3
Lupus erythematodes	1
Observation for epidermophytosis	1
Erysipeloid	2
Cauterisation?	1
Nonspecific erythema	1
Erythema nodosum	3
Crural erythema induratum	1
Herpes zoster	17
Nontraumatic hemarthrosis of the knee	1
Infiltration of the parotid region (sclerema?)	1
Catarrhalia	1

manifest themselves by vivid redness which, as a rule, certainly is not homogeneous, having an unsharp, often scalloped delimitation and, frequently, small red »islets» in the sound skin outside the chief affection. Such »islets» are but rarely observed in erysipelas (cf. Table 9). Besides, the patients with dermatitis and eczema have no or very slight rises of temperature, and their general condition is unaffected. Moreover, a careful anamnesis will in many cases afford information about some noxious agent or other as cause of the skin affection.

In pronounced cases of *erythema solaris* both strong redness and swelling is observed but in most cases there is no rise of temperature, and the general condition is unaffected. The localization of the affection to places exposed to the sun, anamnestic information about »sunbath», and the absence of typical local erysipelas symptoms will moreover afford the correct diagnosis.

Lupus erythematosus should not be difficult to discern from erysipelas, since it generally is a chronic, afebrile affection. Yet there are also some slight, acute cases mostly occurring after much exposure to the rays of the sun, but in this form are observed many larger, sharply delimited and slightly infiltrated red spots of irregular shape with the strongest redness at the borders. The disseminated localization, the secondary formation of scales, and the absence of rise of temperature are the best marks of distinction opposite erysipelas.

An affection which is regularly mistaken for erysipelas is the *erysipeloid* (hog-cholera). During the first days it manifests itself by regular spots and swelling of a vivid red and sharp delimitation, the process just as in erysipelas progressing towards the border and fading in the center. Here the resemblance to erysipelas ceases, however: There is no fever (or, at any rate, very little), and after a couple of days the affection looks quite different, only a slightly swollen, pale bluish redness encircled by a narrow pink border being left. Adding to this information as to the patient's occupation (working with meat, fish or preserves), and the localization to hands and fingers (extremely rare in erysipelas), the diagnosis ought not to be difficult.

Epidermophytosis may be associated with true erysipelas on feet and legs, due to streptococcal infection of the fissures, but recurrent affections resembling erysipelas, yet differing essentially

from erysipelas proper, are reported to be fairly common: No fever, no sharp delimitation, no progressive dissemination, often two separate areas at the same time, and the skin not shining [Traub and Tolmach (17), Sulzberger, Rosterberg and Gootze (15)].

Erythema nodosum and *erythema induratum* are occasionally mistaken for erysipelas. The multiple occurrence and mostly symmetric localization on the legs in the majority of cases permits of correct diagnosis but in isolated cases the single elements may be so well developed that they fuse and thus give rise to an affection reminding of erysipelas. *Erythema induratum* should be still more difficult to mistake for erysipelas, since it is a chronic affection.

The differential diagnosis between erysipelas and *herpes zoster*, particularly *herpes zoster ophthalmicus* may be exceedingly difficult [Ehlers (6)]. In the course of 5 years were 17 patients with herpes zoster admitted to Blegdams Hospital under the diagnosis erysipelas. Among those 17 patients were 15 who suffered from herpes zoster ophthalmicus.

What must be attached particular importance to in the differential diagnosis between herpes zoster ophthalmicus and erysipelas is that the former affection is preceded by neuralgic pains, sharp vertical delimitation in the median line, involvement of the scalp, cornea affection and, often, secondary outbreak on trunk and extremities.

In an isolated case erysipelas was observed as complication of an existing herpes zoster (after scratching in the herpes elements), which may, of course, render correct diagnosis difficult.

A number of those affections which, according to the reports of several authors, may occasionally be mistaken for erysipelas, are not included in this material, for the sake of completeness, however, they shall just be mentioned.

Erythema infectiosum which, during the last 6 months, has occurred fairly often in Copenhagen, may be impossible to discern from erysipelas during the first stages when the patient's face often presents a crimson swelling shaped like a butterfly, with rather sharp, elevated borders, and associated with fever. The diagnosis can be made later, however, when a rash appears all over the body [Bauer (3), Feer (28)].

Now and then the vivid redness round the *vaccination pustules* is mistaken for erysipelas [Ustvedt (22)], but it happens very

Table 13.

Synoptic survey of the subjective and objective symptoms of herpes zoster ophthalmicus and facial erysipelas.

Herpes zoster ophthalmicus	Facial erysipelas
Virtually in all cases preceding neuralgic pains in the region of the first division of the trigeminus.	
As a rule slight rise of temperature about 38°C. Yet, the patient may become highly febrile.	Mostly high fever with cold shiver and vomiting-fits.
Almost always stinging and lancinating neuralgic pains also after the eruption.	Tension and sensation of heat, but now and again real pains too.
The eruption is initiated by redness and swelling of the skin, followed by the formation of small and larger, flat, reddish infiltrates, all appearing at the same time. Subsequently there appear vesicles encircled by a red zone; in isolated cases the vesicles fuse into larger bullae.	Redness and swelling of the skin and, as long as the affection is progressing, sharp, toruloid delimitation too. There do sometimes appear vesicles, though far more frequently, larger bullae.
The affection is sharply delimited by the median line. Yet the edema may extend beyond the median line. Cases of bilateral zoster are extremely rare.	As a rule not confined to one side, nor has the affection ever any sharp vertical delimitation in the median line.
In many cases eruptions on the cornea, and corneal anesthesia which, now and again, does not occur however, before several days have elapsed, and particularly in cases also presenting elements on the tip of the nose.	In case of localization to forehead, nose or cheeks the eyelids often are involved and, hence, very edematous, in some cases even in such a degree that the eye cannot be opened, and inspection (of the eye) may be rendered impossible.
Always conjunctivitis.	Conjunctival injection in some cases.
The scalp is virtually always involved.	The scalp is but rarely affected.
In the majority of cases eruptions of varicelloid herpes elements on trunk and extremities.	

seldom that a child on vaccination is infected with erysipelas; if it does happen, however, the erysipelas will appear fairly rapidly. The usual redness on the contrary appears from 5 to 6 days after vaccination, and it develops together with the pustules. Moreover, it is strongest in the center and without sharp delimitation. *Erythema multiforme* is likewise reported to have been confounded with erysipelas, which is somewhat difficult to understand. *Malignant anthrax* is said to bear resemblance to erysipelas [Ustvedt (22)], but here the swelling is larger, as hard as wood and the diagnosis is evident when the necrotic pustule and the large swelling of the lymph glands appear at the same time.

Now and then *necrosis adiposa neonatorum* has been mistaken for erysipelas at so early a stage of the disease that there was redness over the infiltration and the characteristic elevations had not appeared yet [Bojlen and Petri (5)].

Insect-bites, particularly of bees, in case of pronounced redness may resemble erysipelas but the delimitation characteristic of this affection does not exist. The detection of the very place of bite does not afford the diagnosis, because erysipelas not infrequently originates from an insect-bite.

From the above it is evident that the differential diagnosis of erysipelas may be very difficult, for numerous affections of various kind may be, and have actually been, mistaken for erysipelas but it must be emphasized that phlegmon, lymphangitis, dermatitis artificialis as well as herpes zoster ophthalmicus are the affections which far most frequently are confounded with erysipelas.

Summary.

In a material consisting of 715 patients with erysipelas the usual seasonal variations of incidence are found, i. e. fewest cases in the summer months, most cases in the winter months.

The majority of cases occurred in persons aged 50 to 60 years. There was a considerable female preponderance, particularly of erysipelas on the lower extremities, though also of the other localisations of the affection.

A primary focus of infection was found far more frequently in case of erysipelas on trunk and extremities than in case of facial erysipelas.

The traumatic mode of origin of erysipelas on trunk and extremities is confirmed.

In about 50 per cent of the cases of facial erysipelas a sure or probable traumatic primary focus of infection was detected, and in 8 per cent of the cases a mucosal affection was found to be the sure or probable primary focus of infection.

A great many of the remaining patients with facial erysipelas had had influenza, catarrhalia or angina immediately before they incurred erysipelas, which renders it probable that facial erysipelas relatively often occurs secondarily to an infection of the upper air-passages, the accessory sinuses, the ears and the eyes.

The difficulties of diagnosing erysipelas are discussed in detail.

On the basis of 152 fallacious erysipelas diagnoses on the patients' admission to hospital the differential-diagnostic difficulties are reviewed.

It is emphasized that phlegmon, lymphangitis, artificial dermatitis and herpes zoster ophthalmicus far most frequently are confounded with erysipelas.

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Über den Wert der Magenspülung bei der Behandlung von akuten Vergiftungen.*

Von

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Bei Behandlung der akuten Vergiftung, wo das Gift durch den Mund eingenommen worden ist, versucht man teils soweit möglich die Resorption des eingenommenen Giftes zu verhindern, und teils den resorptiven Giftwirkungen entgegen zu arbeiten.

Zur Hemmung oder Verhinderung der Resorption des eingenommenen Giftes verfügt man über eine Reihe von Methoden:

1. Erzeugung von Erbrechen durch mechanische Auslösung des Brechreflexes oder mit Hilfe von Brechmitteln.
2. Leerung des Magens durch Aspiration.
3. Magenspülung mit grösseren oder kleineren Mengen Wasser (evtl. Kohlensuspension).
4. Zur Entleerung des Darmkanals, Eingabe von schnell wirkenden Abführmitteln, die selbst die Resorption des Giftes nicht beschleunigen.

* Für die Barbitursäuren werden im folgenden die angeführten dänischen Pharmakopoe-namen benutzt:

Diemal = Diäthylbarbitursäure (Veronal u. ähnl.)

Phenemal = Phenyläthylbarbitursäure (Luminal u. ähnl.)

Diallynal = Diallylbarbitursäure (Dial u. ähnl.)

Allypropynal = Allylisopropylbarbitursäure (Isonal, Numal u. ähnl.).

5. Eingabe von spezifischen Gegengiften, die den Giftstoff chemisch zu ungiftigen oder unlöslichen Verbindungen umbilden.

6. Eingabe von Tierkohle (carbo medicinalis), die zahlreiche Gifte adsorbiert und dadurch deren Resorption im Darmkanal verhindert oder verzögert (»Adsorptionstherapie«).

Häufig werden mehrere dieser Methoden kombiniert. Die zur Zeit am häufigsten angewandte Behandlung der meisten Vergiftungen besteht in der Magenspülung (evtl. mit Kohlensuspension) und nachfolgender Eingabe von carbo medicinalis und salinischen Abführmitteln. Brechmittel sind in den letzten 50 Jahren nur sehr wenig angewandt worden, und die Magenspülung war in dieser Zeit die hauptsächlich angewandte Therapie. Bei den relativ wenigen Vergiftungen, wo wirksame spezifische »Antidoten« zur Verfügung stehen, ist deren Anwendung immer indiziert.

Die Benutzung von Kohle zur Behandlung der akuten Vergiftung ist alt (Touéry etwa 1830; Garrod 1858), aber systematische Anwendung hat Kohle erst auf Grund der Untersuchungen von Wiechowski (1910, 1915) über die Wirkungsweise der Kohle und durch Starkensteins eindringliche Betonung der Bedeutung der Adsorptionstherapie erhalten, ein Gesichtspunkt, der völlig in Übereinstimmung mit unserer Auffassung steht. Über die Wirkungsweise der Kohle und ihre Bedeutung bei Behandlung von akuten Vergiftungen hat A. Harrestrup Andersen hier im pharmakologischen Institut umfassende Untersuchungen ausgeführt, die später veröffentlicht werden sollen.

Die Auffassung der Mehrzahl der Ärzte über die Bedeutung der Magenspülung bei Behandlung der akuten Vergiftung kann wohl folgendermassen formuliert werden: In Fällen von akuter Vergiftung muss die Unterlassung der Magenspülung als ein Kunstfehler betrachtet werden, soweit es sich nicht um Vergiftung mit starken Basen oder Säuren handelt, oder soweit nicht sehr lange Zeit seit der Eingabe des Giftes verstrichen ist. Diese Anschauung begründet sich wahrscheinlich darauf, dass man es als selbstverständlich angesehen hat, dass ein Stoff der in den Magen gelangt ist, auch wieder durch Spülung entfernt werden kann, und fernerhin darauf, dass man bei einer Reihe von Vergiftungen direkt das eingenommene Gift im Spülwasser gefunden hat, wo es durch Farbe, Geruch oder in anderer Weise zum Vorschein gekommen ist. Soweit uns bekannt, liegen quantitative systematische Untersuchungen über die Grösse

der Giftmengen, die man tatsächlich durch Magenspülung entfernen kann, nicht vor.

Die Literaturangaben über die zweckmässigste Technik bei der Spülung, über die Menge der anzuwendenden Flüssigkeit u. a. sind spärlich und widerspruchsvoll. Häufig wird die Spülung mit sehr grossen Flüssigkeitsmengen vorgenommen; Popper (1933) empfiehlt Spülung mit 10—40 Liter Wasser. Nur ein einzelnes toxikologisches Handbuch äussert Zweifel über die Bedeutung der Spülung (Starkenstein, Rost und Pohl 1929) und führten an: »Während der Magenspülung kann die Resorption des noch nicht ausgespülten Giftes weiter fortschreiten und durch das Spülwasser unter Umständen sogar eine Lösung noch nicht gelöster Giftmengen erfolgen, die dann durch den Pylorus in den Darm gelangen können.»

Der Zweck der vorliegenden Arbeit war die Beschaffung eines grossen Materiales zu einer quantitativen Beurteilung der Bedeutung der Magenspülung bei der akuten Vergiftung, wobei in der Hauptsache Wert darauf gelegt wurde zu untersuchen, *wie grosse Mengen des eingenommenen Giftes tatsächlich mit der Spülflüssigkeit herausbefördert werden können*. Da die Literatur über das genannte Problem nur sehr spärlich ist, erschien es uns berechtigt im Anschluss an unsere Untersuchungen die ganze Frage verhältnismässig ausführlich zu behandeln, und hierbei auch die historische Seite des Problems zu berücksichtigen.

1. Historischer Überblick.

Obwohl man schon im griechischen Altertum Versuche zur künstlichen Erzeugung des Erbrechens gemacht hat, versuchte man erst in der römischen Kaiserzeit systematisch Methoden zur Leerung des Magens zu finden. Brechmittel waren bekannt, aber da die Indikation zur Erzeugung von Erbrechen fast ausschliesslich die Nachwirkungen nach »lukullischen« Mahlzeiten war, und da Brechmittel in gewissen Fällen nur Übelkeit mit sich führten, versuchte man anstatt dessen den Brechreflex durch mechanische Reize auszulösen. Hierzu wurden Brechfedern (*pinna*) (8—10 in Oel getauchte Schwanzfedern von Gänsen) und andere komplizierte Methoden benutzt. Diese Methoden sollen auch bei Opiumvergiftungen im ersten Jahrhundert vor Christi (Oser 1887) benutzt worden sein.

Am Ende des 17. Jahrhunderts wurde der Gebrauch eines Apparates, der sogenannten »Magenbürste« (»Magenkrätzer«, *excucia ventriculi*) eingeführt, welche aus einer Magensonde aus Fischbein bestand und an der Spitze mit einer kleinen Bürste versehen war, die durch Auf- und Abwärtsbewegen die »Magen-schleimhaut säubern« sollte. Eine Zeitlang wurde dieser Apparat viel angewandt, hat aber bei Vergiftungen anscheinend keine Verwendung gefunden (Leube, 1879).

1776 empfahl der berühmte Chirurg John Hunter als erster die Anwendung von hohlen, röhrenförmigen und biegsamen Magen-sonden, um lokalreizende Stoffe wie Terpentin u. ähnliche unmittelbar in den Magen zur Wiederbelebung von Ertrunkenen einführen zu können. Kurz darauf wurde die Magensonde sowohl zur Einführung von Flüssigkeiten in den Magen, als auch zur Aspiration aus dem Magen unter Benutzung einer gewöhnlichen Spritze mit Stempel benutzt. Die Kombination dieser beiden Eingriffe zum Zwecke der Magenspülung war nahe liegend, und zum ersten Male wurde dieser Gedanke von dem englischen Wundarzt F. Bush (veröffentlicht 1822) in der Praxis verwirklicht, der in mehreren Fällen von Opiumvergiftung den Magen unter Benutzung einer einfachen Spritze mit Stempel spülte (zit. nach Leube S. 20). Im zweiten Jahrzehnt des vorigen Jahrhunderts erschienen verschiedene, komplizierte und sinnreiche *Magenpumpen*, die von Jukes, Ward, Read u. a. konstruiert worden waren (zit. nach Leube S. 21), wovon namentlich die von Read angegebene in weiten Kreisen bekannt wurde. Diese wird z. B. in der Buchner'schen Toxikologie aus dem Jahre 1827 und in der dänischen Toxikologie von Otto (1838) ausführlich behandelt. Eine ausführliche Beschreibung mit Abbildungen der Weiss'schen Magenpumpe findet sich bei Gräfe (1826).

Die verschiedenen Methoden und Instrumente erreichten keinen grösseren Anwendungsbereich und gerieten allmählich in Vergessenheit bis von Kussmaul (1867—69) die Magenspülung bei Behandlung der Magendilatation dringlich empfohlen wurde. Die komplizierte »amerikanische Magenpumpe« und ähnliche Apparate, die Kussmaul benutzt hatte, wurden jedoch bald wieder verlassen und durch die Arbeiten von Jürgensen (1870), Ploss (1870), Rosenthal (1870) und Hodgen (1870) wurde das Prinzip des Hebers in die Technik des Magenspülens eingeführt, wenn auch immer noch

in komplizierterer Form als es heute verwendet wird. Die Verwendung von Gummi anstatt des Hartgummis als Material für Magensonden wird erstmalig von Oser (1875) und von Ewald (1875) erwähnt. Am Ende des vorigen Jahrhunderts wurde auf Empfehlung des bekannten Toxikologen Lewins (1895) die sogenannte »Klyso-Pumpe« (ein Gummiballon der mit zwei gleichgerichteten Ventilen versehen ist eingeführt, die auch heute noch einige Anwendung findet.

Die heutzutage fast ausschliesslich zur Magenspülung angewandte Methode, wobei nur die Magensonde in Verbindung mit einem langen Gummischlauch, der in einem grossen Glastrichter endet, angewandt wird, wurde schon 1823 von Sommerville beschrieben, ohne dass diese Methode zunächst weitere Anwendung fand. Ewald (1875) benutzte dieses moderne »Trichter-Heber-Prinzip«, das auch in der Toxikologie von Kobert (1887) behandelt wird.

Bei der Vergiftungsbehandlung dominierte die Anwendung von Brechmitteln lange Zeit über die Magenspülung, die gewöhnlich nur dann benutzt wurde, wenn die Brechmittel versagten oder aus anderen Gründen nicht angewandt werden konnten. Aus den toxikologischen Handbüchern der verschiedenen Zeiten geht eindeutig hervor, dass die Magenspülung erst seit Ende des vorigen Jahrhunderts die hauptsächliche Behandlungsmethode von Vergiftungen geworden ist.

2. Die im Magen gefundene Giftmenge bei Personen die an Vergiftungen ohne vorausgegangene Magenspülung gestorben sind.

Zur Beurteilung der Frage des Wertes der Magenspülung ist es von Interesse zu wissen, wie gross die im Magen vorhandenen Giftmengen in Fällen von Vergiftungen sind. Wie später gezeigt wird, kann eine Untersuchung der Spülflüssigkeit keine Klärung dieser Frage bringen. Es bleibt daher nur die Möglichkeit der Bestimmung der Giftmenge im Mageninhalt von an Vergiftungen gestorbenen Personen.

Von den in den letzten Jahren zur gerichtsmedizinischen Untersuchung im pharmakologischen Institut analysierten Fällen wurden alle die ausgewählt, die an den in Tabelle 1—3 angeführten

Tabelle 1.

Giftmenge im Magen von an Schlafmittelvergiftung gestorbenen Menschen. Keine Magenspülung. Diemal = Diäthylbarbitursäure; Phenemal = Phenyläthylbarbitursäure; Diallynal = Diallylbarbitursäure; Allypropynal = Allylisopropylbarbitursäure.

Laufende Nummer	Art des Giftes	Zeitintervall zwischen Einnahme des Giftes und Tod	Menge des Mageninhalts in ml.	Im Mageninhalt gefunden in g	Bemerkungen
605	gemischte Barbitursäuren	ca. 12 St.	27	0.081	
513	Diemal	< 6 St.	38	2.87	
634	Diemal	ca. 30 St.	73	0.008	
665	Diemal	ca. 48 St.	425	0.011	
425	Phenemal	14 St.	10	0	
489	Phenemal	ca. 20—24 St.	44	0.28	
659	Phenemal	ca. 30 St.	46	0.005	
660	Phenemal + Morphin	ca. 2 St.	210	{ 2.30 Diemal 0.129 Morphin	
435	Allypropynal	ca. 12 St.	138	1.37	
463	Allypropynal	< 5 St.	220	0.011	
483	Allypropynal	ca. 10 St.	120	1.05	
636	Allypropynal	12—15 St.	38	0.023	
629	Allypropynal + Kloralhydrat	4 St.	110	{ 0.06 Allypr. 0.40 Kloral.	
391	Diallynal	ca. 24 St.	86	0	
535	Diallynal	ca. 48 St.	62	0.004	
555	Diallynal	ca. 12 St.	ca. 250 ¹	ca. 30 g ¹	in 23 ml 3.0 g gefunden
589	Diallynal	ca. 30 St.	205	0.009	
630	Diallynal	ca. 28 St.	44	0.007	
619	Diallynal + Morphin	ca. 12—18 St.	146	{ 0.043 Diallynal 0.0003 Morphin	
577	Aethylallylbarbitursäure	ca. 48 St.	7	0	
365	Cibalgin	ca. 2 St.	1200	{ 2.08 Diallynal 12.7 Amidopyrin	57—58 Tabletten entsprechend

Giften gestorben sind, und bei denen mit Sicherheit bekannt war, dass eine Magenspülung oder eine andere Behandlung, die die Leerung des Magens bezweckte, nicht vorgenommen worden war. Es handelt sich hierbei um Personen, die tot aufgefunden wurden, oder die während des Transportes zum Hospital gestorben sind, oder bei denen Magenspülung nicht vorgenommen wurde, weil

¹ Nur etwa 1/10 des Mageninhalts wurde zur Untersuchung geschickt. Die Gestorbene war Krankenschwester.

Tabelle 2.

Giftmenge im Magen von an verschiedenen Vergiftungen gestorbenen Menschen. Keine Magenspülung. Arsen war in allen Fällen in Form von Lösungen eingenommen worden, die zur Reinigung des Viehes benutzt werden.

Laufende Nummer	Art des Giftes	Zeitintervall zwischen Einnahme des Giftes und Tod	Menge des Magen-inhalts in ml.	Im Magen-inhalt gefunden in g	Bemerkungen
127	Arsenik ¹	ca. 48 St.	300	0.0005 As	
154	»	?	257	0.839 »	
204	»	4 St.	360	0.047 »	
377	»	< 12 St.	850	0.0008 »	
490	»	ca. 24 St.	70	0.064 »	
604	Cyanwasserstoff	?	27	0.0002 HCN	
37	Cyankalium-Cyannatrium	< 2 St.	75	0.021 »	
83	»	ca. 1—2 St.	504	0.011 »	
84	»	?	14	0.002 »	
108	»	< 1 St.	80	0.011 »	
116	»	?	14	0.0003 »	
223	»	?	66	0.007 »	
638	»	?	700	0.019 »	
347	Nikotin	wenige Minut.	165	1.97 Nikotin	
361	»	?	285	0.29 »	
398	»	wenig. Minut.	15	0.024 »	
406	»	?	60	2.32 »	
457	»	?	22	0.064 »	
480	»	wenig. Minut.	330	6.80 »	
518	»	wenig. Minut	390	0.75 »	
542	»	?	300	3.42 »	
576	»	wenig. Minut.	110	0.17 »	
587	»	?	17	0.128 »	
610	»	?	40	1.01 »	
615	»	< 10 Min.	450	6.70 »	
661	»	?	160	5.24 »	
322	Nitrobenzol	2—4 St.	190	5.74 Nitrob.	
433	Strychnin	1—2 St.	414	0.103 Strych.	

dies wegen der langen Zeit, die seit Einnahme des Giftes verstrichen war, oder aus anderen Gründen, nicht mehr indiziert war. Tabelle 1 enthält eine Zusammenstellung der Fälle von Schlafmittelver-

¹ Zur Reinigung von Vieh benutzte Arsenlösung.

Tabelle 3.

Menge von Strychnin (*Str.*), Chinin (*Chin.*) und Eisen (berechnet als Fe_2O_3) im Magen von Menschen, die nach Einnahme von Easton Sirup Tabletten gestorben sind. Keine Magenspülung. Eine Tablette enthielt zu der betreffenden Zeit 2 mg Strychninphosphat (etwa 1.8 mg Strychnin entsprechend) und 5 cg Chininphosphat.

Nr.	Zeit zwischen Gifteinnahme u. Tod	Mageninhalt Menge in ml.	Im Mageninhalt		Im Darmkanal		Alter d. Gestorbenen Jahre
			gefundene Substanz g	gefundene Eisenmenge in Tabl. umgerechnet	gefundene Substanz g	gefundene Eisenmenge in Tabl. umgerechnet	
145	ca. 1 St.	37	0.274 Chin. 0.007 Str.	—	—	—	6
286	ca. 1 St.	220	0.622 Fe_2O_3	21 Tabl.	—	—	53
339	ca. 1 St.	91	0.026 Fe_2O_3	ca. 1 Tabl.	0.424 Fe_2O_3	14 Tabl.	7
380	?	118	0.211 Fe_2O_3	6 ½ Tabl.	1.08 Fe_2O_3	33 Tabl.	25
453	?	204	0.010 Str. 0.256 Chin. 0.450 Fe_2O_3	13 ½ Tabl.	1.59 Fe_2O_3	48 Tabl.	45
465	ca. 1 St.	280	0.0003 Str. 0.266 Fe_2O_3	8 Tabl.	0.242 Fe_2O_3	7 ½ Tabl.	2 ¾

giftungen, Tabelle 2 eine solche von Vergiftungen mit Arsen, Blausäure und Nikotin und Tabelle 3 Vergiftungen mit Easton-Sirup-Tabletten, die später näher beschrieben werden.

Die chemisch-analytische Technik bei den vorgenommenen Bestimmungen war die hier im Institut bei gerichtsmedizinischen Untersuchungen übliche, (vgl. auch den folgenden Abschnitt).

Die Analyse von *Schlafmittelvergiftungen* (Tabelle 1) zeigen sehr variierende Ergebnisse. Wenn man auch annehmen muss, dass ein Teil der gefundenen niedrigen Werte dadurch bedingt ist, dass mehrere Tagen zwischen der Einnahme des Giftes und dem Eintreten des Todes vergangen sind, können die stark schwankenden Resultate nicht allein durch die verschiedene Zeit erklärt werden, die vor dem Eintritt des Todes verstrichen war. Dieses geht eindeutig aus der Tabelle hervor. Die Grösse der eingenomme-

nen Dosis ist natürlich von wesentlicher Bedeutung, diese war aber nicht bekannt; in allen Fällen war sie jedoch so gross, dass sie für den betreffenden tödlich war. In 6 von 21 Fällen von Schlafmittelvergiftung wurde im Magen mehr als 1 g gefunden und in 3 dieser Fälle ist mit Sicherheit bekannt, dass mindestens 10–12 Stunden zwischen der Einnahme des Giftes und dem Eintreten des Todes verstrichen sind (1.05 g/10 Stunden; 1.37 g/12 Stunden; ca. 30 g/ca. 12 Stunden). Im Fall Nr. 555, wo etwa 30 g Diallynal gefunden wurden, handelte es sich um eine Krankenschwester, die eine ausserordentlich grosse Dosis eingenommen haben muss.

Die angeführten Fälle von Schlafmittelvergiftungen zeigen, dass bei einer Reihe von Fällen wesentliche Giftmengen selbst dann im Magen auftreten können, wenn auch mehrere Stunden nach der Einnahme des Giftes verstrichen sind. Dieser Befund sollte ohne weiteres eine gute Grundlage für die Ausführung der Magenspülung sein, die auch dann ausgeführt werden sollte, wenn lange Zeit seit der Eingabe des Giftes vergangen ist.

Bei *Zyanidvergiftungen* (Tabelle 2) ist der Tod in allen Fällen, wo nähere Einzelheiten bekannt waren, nach 1–2 Stunden oder nach kürzerer Zeit eingetreten. In den anderen Fällen kann man wahrscheinlich annehmen, dass der Tod ebenso schnell eingetreten ist. Im Mageninhalt wurden 0.3 bis 21 mg HCN gefunden, d. h. kleine Mengen, wenn man bedenkt, dass das Gift meistens in Form von wesentlichen Mengen starker Lösungen von Zyankalium oder Zyannatrium eingenommen worden ist. Die schnelle Resorption des im Magen von der Salzsäure freigemachten Zyanwasserstoffs erklärt wahrscheinlich dieses Verhalten.

In den meisten Fällen von *Nikotinvergiftung* (Tabelle 2), wo die Zeit des Eintritts des Todes bekannt war, betrug diese nur ganz wenige Minuten und wahrscheinlich war die Zeit in allen übrigen Fällen von gleicher Grössenordnung. Von den 13 Fällen wurde nur in einem Fall (Nr. 398) im Magen weniger als die geringste tödliche Dosis Nikotin gefunden (zu 25–30 mg geschätzt); in der Mehrzahl der Fälle wurde wesentlich mehr als eine tödliche Dosis gefunden, und in 7 von 13 Fällen war mehr als 1 g vorhanden (1.01–6.8 g). Die Ursache hierfür ist wohl in der Hauptsache die sehr kurze Zeit, die zwischen der Einnahme des Giftes und dem Tode vergeht und deshalb wird eine Magenspülung nur äusserst selten Bedeutung haben können.

Die Anzahl der Fälle von Vergiftungen mit Easton-Syrup-Tabletten ist klein (vgl. Tabelle 3), aber enthält trotzdem eine Reihe von wertvollen Aufschlüssen. Die in den Tabletten vorhandene Eisenmenge bleibt bei der kurzen Zeit, die zwischen Einnahme der Tabletten und Eintritt des Todes vergeht, in unveränderter Menge im Verdauungskanal, da weder Resorption oder Ausscheidung mit den Fäces sich geltend machen kann. Man kann daher die Gesamtmenge der eingenommenen Tabletten mit grosser Genauigkeit aus dem Eisengehalt (siehe Spalte 5 und 7 der Tabelle 3) feststellen und die Verteilung des Eisens zwischen Magen und Darm beim Eintritt des Todes, der in der Regel eine Stunde nach Einnahme der Tabletten erfolgt, bestimmen.¹ Aus der Tabelle ist ersichtlich, dass in 3 von den 4 vollständig untersuchten Fällen wesentlich grössere Mengen im Darmkanal als im Magen gefunden worden sind. *Der grösste Teil der eingenommenen Tabletten ist also im Laufe von einer Stunde in den Darm gelangt.* In einer Reihe von Fällen wurden aber trotzdem im Magen beträchtliche Eisenmengen gefunden. Die im Magen gefundenen Strychnin und Chininmengen sind geringer als die auf Grund der Eisenmenge berechnete Tablettenanzahl; dies bedeutet, dass Strychnin und Chinin, die als wasserlösliche Salze vorhanden sind, den Magen noch schneller verlassen als Eisen. Die im Magen gefundenen Giftmengen sind aber so gross, dass von vorneherein eine Magenspülung als indiziert angesehen werden muss.

3. Die Giftmenge im Spülwasser der Magenspülung von 80 Personen mit akuten Vergiftungen, vorwiegend Schlafmittelvergiftungen.

Wie zuvor erwähnt, liegen soweit uns bekannt, keine systematischen Untersuchungen über die Giftmengen, die durch eine Magenspülung entfernt werden können, vor.

Wenn solche Untersuchungen von Wert sein sollen, muss man verlangen, dass die Spülung in allen untersuchten Fällen auf gleichartige Weise vorgenommen wird. Deshalb wurde das ganze vorliegende Material von der psychiatrischen Abteilung des Bispebjærg

¹ Auf Grund der allgemeinen Erfahrungen bei Strychninvergiftungen kann man annehmen, dass die Vergiftung in keinem Fall wesentlich länger als eine Stunde gedauert hat.

Hospitals gesammelt, was den grossen Vorteil hat, dass sämtliche Vergiftungen sofort nach der Einlieferung in das Hospital von einem wohlgeübten und festen Personal behandelt wurden, dem wir für die Sorgfalt, mit der die Arbeit ausgeführt wurde, ausserordentlich zu Dank verpflichtet sind. Die Aufsammlung der Spülflüssigkeit nach der im folgenden angegebenen Methode, sowie die Einsammlung der zugehörigen klinischen Daten wurde von dem einen von uns geleitet (Harstad). Die Untersuchung läuft seit über 2 Jahren.

Allgemeiner Versuchsplan.

Bei sämtlichen Patienten, die mit dem Krankheitsbilde einer akuten Vergiftung in der Versuchsperiode in die psychiatrische Abteilung eingeliefert wurden, wurde sofort eine Magenspülung vorgenommen.

Die Spülung geht in folgender Weise vor sich: Der Patient wird in horizontaler Lage auf dem Untersuchungslager angebracht, in gewissen Fällen mit herabhängenden Kopf (s. S. 510). Die Spülung erfolgt in der üblichen Art und Weise durch eine weiche Magensonde, die mit einem Gummischlauch und einem grossen Glas-trichter versehen war, d. h. nach dem Heberprinzip. Zur Spülung diente gewöhnliches lauwarmes Wasser, und jedesmal wurde genau 1 Liter Wasser, insgesamt 10 Liter Wasser in den Magen gegossen. Nach jeder einzelnen Eingiessung von 1 Liter, wurde die aus dem Magen ausgelaufene Flüssigkeit gesammelt. Die Spülflüssigkeit wurde dann in 5 Teile geteilt, deren Menge jeweils gemessen wurde. Die erste Portion bestand aus der Flüssigkeitsmenge, die nach der Eingiessung von dem ersten Liter aus dem Magen gesammelt wurde; die zweite Portion enthielt die Flüssigkeitsmenge, die nach dem Eingiessen des zweiten Liters aus dem Magen geholt wurde, die dritte Portion enthielt was nach dem dritten und vierten Liter gesammelt wurde, die vierte Portion die Spülflüssigkeit nach dem 5. 6. und 7. Liter und die fünfte Portion die Spülflüssigkeit von dem 8. 9. und 10. Liter. Die fünf Flaschen wurden verschlossen und im Eisschrank aufbewahrt, bis sie sobald wie möglich zum pharmakologischen Institut geschickt werden konnten, wo die einzelnen Spülflüssigkeitsportionen jede für sich analysiert wurden.

Nach beendigter Spülung wurde Kohle und Magnesiumsulfat eingegeben und die Patienten sonst wie gewöhnlich behandelt.

Durch ausfragen der überlebenden Patienten wurde versucht, so weitgehende Aufschlüsse wie möglich über die *Menge* des eingenommenen Giftes, sowie über den *Zeitpunkt* der Einnahme zu erhalten. Soweit möglich wurde versucht entsprechende Angaben auch über die nicht überlebenden Patienten zu erhalten. In den meisten Fällen, in denen der Tod eintrat, wurde der bei der Sektion erhaltene Magen- und Darminhalt auch untersucht.

Analytische Technik.

Wenn nicht von vorneherein Aufschlüsse oder Vermutungen vorlagen, dass es sich um flüchtige Gifte handelte, wurde die Untersuchung auf folgende Weise vorgenommen:

Die einzelnen Portionen der Spülflüssigkeit werden fast bis zur völligen Trockenheit im Wasserbade eingedampft und gründlich mit absolutem Alkohol extrahiert. Nach dem Filtrieren wird der Alkohol im Vakuum abdestilliert und der Rückstand in Wasser gelöst. Aus dieser Lösung werden dann die verschiedenen Giftstoffe isoliert.

Barbitursäuren werden durch Schütteln mit Äther bei saurer Reaktion isoliert. Der Äther wird abdestilliert und der eventuel vorhandene Rückstand durch die von Fleury (1925) angegebene Merkurisulfatfällung gereinigt. Die auf diese Art isolierten Barbitursäuren werden quantitativ durch Wiegen bestimmt und nach ihrem Schmelzpunkt identifiziert.

Phenacetin wird auf die gleiche Art wie die Barbitursäuren isoliert aber durch Umkristallisation gereinigt und quantitativ durch Wiegen bestimmt.

Salicylsäure (Acethylsalizylsäure) wird auf die gleiche Art wie die Barbitursäuren isoliert aber ebenso wie Phenacetin durch Umkristallisation gereinigt. Die erste Eindampfung der Spülflüssigkeit wird jedoch unter Berücksichtigung der Flüchtigkeit der freien Salizylsäuren bei basischer Reaktion vorgenommen. Die quantitative Bestimmung erfolgt durch Wägen und Titration.

Chinin wird aus der durch Eindampfung, Überführung auf Alkohol etc. erhaltenen wässrigen Lösung, die erst mit Äther bei saurer Reaktion geschüttelt wird, isoliert. Das Chinin wird dann bei Natron-alkalischer Reaktion mit Äther geschüttelt und quantitativ durch Wiegen und Titration bestimmt.

Die flüchtigen Gifte werden folgendermassen bestimmt:

Nitrobenzol wird durch Destillation mit Wasserdampf mit nachfolgendem Schütteln des Destillats mit Äther isoliert. Die quantitative Bestimmung erfolgt durch Wiegen des Rückstandes nach der Destillation des Äthers und nach dem Trocknen der Substanz.

Tetrachlormethan wird durch Durchlüftung einer Portion des Spülwassers bestimmt. Der Luftstrom der durch die Flüssigkeit geblasen wird, wird auf etwa 1000 Grad erwärmt und das hierdurch freigemachte Chlor durch Absorption in einer Silbernitratlösung von bekannter Stärke und nachfolgender Titration der übriggebliebenen Silbernitratmenge bestimmt.

Bei Analysen des Magen- und Darminhaltes wird dieser zunächst mehrfach mit warmem Alkohol extrahiert. Die alkoholischen Extrakte werden filtriert und der Alkohol im Vakuum abdestilliert. Der Rückstand wird in Wasser gelöst und die weitere Behandlung ist wie die der Spülflüssigkeit.

Insgesamt wurde Spülflüssigkeit von etwa 100 Patienten untersucht und so etwa 1000 Liter Spülflüssigkeit analysiert.

Ergebnisse.

Eine Anzahl Fälle der hundert untersuchten Patienten mit akuten Vergiftungen konnten bei Bearbeitung des Materials nicht berücksichtigt werden, entweder weil sich später ergab, dass die Patienten ein anderes Gift eingenommen hatten als dasjenige, welches man nachzuweisen versuchte, oder weil später Zweifel auftraten, ob es sich überhaupt um eine Vergiftung gehandelt hatte. Nach Abzug dieser Fälle enthält das Material Untersuchungen an 80 Patienten mit sicher gestellten Vergiftungen, und die verschiedenen Vergiftungen sind folgendermassen verteilt:

Eingenommenes Gift	Anzahl
Barbitursäurederivate	71
Bromisoval (= Bromural)	1
Opiumalkaloide	1
»Kopfschmerztabletten«	3
Chinin	2
Nitrobenzol	1
Tetrachlormethan + etwas Barbitursäure	1
	<hr/> 80

In einem Teil der Barbitursäurefälle waren ausser Barbitursäure andere weniger giftige Stoffe (Phenazetin u. ähnl.) eingenommen worden, aber in diesen Fällen wurde die Spülflüssigkeit nur auf Barbitursäuren analysiert. Am häufigsten war *eine* Barbitursäure eingenommen worden, in einem Teil der Fälle Mischung von mehreren Barbitursäuren. Die untersuchten Fälle sind in den Tabellen 4 und 5 zusammengestellt, wo nur die notwendigsten Daten aufgeführt sind.

Tabelle 4.

Giftmenge im Spülwasser von 71 Patienten mit Barbitursäurevergiftung und einem Fall von Bromuralvergiftung (zu unterst in der Tabelle). Im Falle Nr. 3 hat der Patient vor der Spülung erbrochen. In dem Erbrochenen fand sich 1.1 g Aethylallylbarbitursäure.

Nr.	Eingenommene Barbitursäure in Gramm	Zeit zwischen Gifteinnahme und Magenspülung	Im Spülwasser gefunden Gramm	Zustand d. Pt. bei Magenspülung	Bemerkungen
1	?	1 Stunde	0.09	Bewusstlos	{Exitus letalis (Diemal)
2	6	9—10 »	0	»	
3	7.5	3 »	0.12	Benommen	
4	4	10 »	0.007	»	{Exitus letalis (gemischte)
5	?	4 »	0	»	{Exitus letalis (verschiedene Barbitursäuren)
6	10	? »	0	Bewusstlos	
7	1.3	1 »	0.07	»	
8	1	3 »	0.09	Benommen	{Exitus letalis (Allypropynal)
9	1.1	2½ »	0	Bewusstlos	
10	6	¾ »	0.21	»	
11	3	?	0	»	{Exitus letalis (Diemal)
12	?	?	0	Benommen	
13	2	1¾ »	0.13	Bewusstlos	
14	?	4½ »	0.003	»	{Exitus letalis (Diallynal)
15	1	2 »	0	»	
16	1.4	7½ »	0	»	
17	1.5	3 »	0	Benommen	{Exitus letalis (Diallynal)
18	1	2 »	0	Bewusstlos	
19	5	3½ »	0	»	
20	7.5	24 »	0	»	{Exitus letalis (Diallynal)
21	?	15 »	0.003	»	
22	1.8	12 »	0	Benommen	
23	3.5	?	0.002	Bewusstlos	{Exitus letalis (Diallynal)
24	2	?	0.05	»	
25	3	6 »	0	»	
26	1.1	8 »	0.02	»	{Exitus letalis (Diallynal)
27	?	?	0.03	»	
28	?	6 »	0	»	
29	2.2	3 »	0	»	

Tabelle 4 (Fortsetzung).

Nr.	Eingenommene Barbitursäure in Gramm	Zeit zwischen Gifteinnahme und Magenspülung	Im Spülwasser gefunden Gramm	Zustand d. Pt. bei Magenspülung	Bemerkungen
31	4	?	0.71	Bewusstlos	{Exitus letalis (Allypropynal + Diallylnal aa pts
32	2	1 Stunde	0.09	»	{Exitus letalis (Diallylnal)
33	1	3 »	0	»	
34	1.7	3 ½ »	0.003	Benommen	
35	1	1 »	0.09	»	
36	1.3	2 »	0.07	»	
37	5	2 ½ »	0.03	Bewusstlos	{Exitus letalis (Allypropynal + Diallylnal aa pts)
39	6	3 »	0.03	»	
40	4	3 »	0.05	»	
41	?	?	0	Benommen	
43	6	8 »	0	Bewusstlos	
44	2.4	7 »	0	»	
45	5.2	4 ½ »	0.26	»	
46	?	2 »	0	»	
47	4	3 »	0.05	»	
48	1.4	1 ½ »	0	Wach	
49	1.8	20 »	0	Bewusstlos	
50	3.5	4 »	0	»	
52	1.3	1 »	0	Wach	
53	4.5	2 »	1.14	Bewusstlos	{Exitus letalis (Atylallyl- barbitursäure)
54	?	?	0	»	{Exitus letalis (gemischte)
55	1.5	1 »	0	»	
56	2.5	?	0.11	»	
57	?	40 »	0	»	{Exitus letalis (gemischte).
58	2	1 »	0.01	»	
59	0.8	2 ½ »	0	Benommen	
61	?	?	0	Bewusstlos	{Exitus letalis (Allypropynal)
62	1.5	2 ¼ »	0.14	Benommen	

Tabelle 4 (Fortsetzung.)

Nr.	Eingenommene Barbitursäure in Gramm	Zeit zwischen Gifteinnahme und Magenspülung	Im Spülwasser gefunden Gramm	Zustand d. Pt. bei der Magenspülung	Bemerkungen
63	0.8	19 Stunde	0	Bewusstlos	{Exitus letalis (Diallylnal)}
64	2.8	2 ½ »	0.06	»	
65	1	2 ½ »	0	»	
66	1.5	1 »	0.01	»	
67	5	4 »	0.11	»	
68	2	½ »	0.07	»	{Exitus letalis (Allypropynal)}
69	?	1 »	0.04	»	
70	?	?	0.05	»	
71	?	?	0.22	»	
73	0.8	3 »	0	»	
74	2.8	38 »	0	Benommen	{Exitus letalis (gemischte Barbiturs.)}
75	3.8	3 »	0	»	
77	3	3 »	0	»	
79	?	3 »	0	Bewusstlos	
60	Bromural 6 g	?	0	Benommen	

In 16 Fällen führte die Vergiftung zum Tode; es handelt sich in allen Fällen um Barbitursäurevergiftungen. Die Mortalität bei diesen war also hiernach 23 Prozent.

In der Mehrzahl der Fälle handelt es sich um schwere oder ziemlich schwere Vergiftungen, was auch daraus ersichtlich ist, dass 53 der 71 mit Barbitursäure vergifteten bei Einlieferung in das Hospital bewusstlos und meist reaktionslos waren. In 16 Fällen waren die Patienten verwirrt und im Dämmerzustand und nur 2, die kurz nach der Einnahme des Giftes eingeliefert worden waren, waren wach.

Bei den an der Vergiftung gestorbenen Patienten, wo in der Spülflüssigkeit keine Barbitursäure vorhanden war, wurde die Diagnose Barbitursäurevergiftung durch Analyse des Darminhaltes bestätigt.

Die vorgenommenen Analysen zeigen, dass in der grossen Mehrzahl der Fälle die Spülflüssigkeit entweder überhaupt kein Gift oder

Tabelle 5.

Giftmenge im Spülwasser von 8 Patienten mit verschiedenen akuten Vergiftungen.

Nr.	Gifteinnahme	Zeit zwischen Gifteinnahme und Magenspülung	Im Spülwasser gefunden. Gramm	Zustand d. Pt. bei d. Magenspülung
30	Phenazetin 25 g Acetylsalizyls. 25 „ Codein 1 „	1 St.	1.44 g Phenazetin u. Salizylsäure	Benommen Leicht zyanotisch
38	Opium ? g	2 St.	0	Benommen
42	Phenazetin 50 g	?	0.08	Benommen, leicht zyanotisch und blass
51	Phenazetin, Antipyrin, Acetanilid, Coffein. ? g	?	0	Bewusstlos, blass, zyanotisch. Resp. oberflächlich.
72	Chininsulfat 10 g	1 ½ St.	1.24	Augen u. Ohrensymptome. Wach.
76	Nitrobenzol ? g	< 2 St.	0.27	Benommen, blass, unruhig.
78	Tetraklormetan, 1 Weinglas + Diallylnal 0.4 g	9 St.	0 Barbiturs. 0 Tetrachlor.	Benommen und schläfrig
80	Chininsulfat 5 g	3 ½ St.	0.61	Wach, schwerhörig.

nur geringe Mengen des Giftes enthalten hat. In 40 von 80 Fällen enthielt die Spülflüssigkeit kein Gift. Aus Tabelle 6 ist ersichtlich, dass bei 62 Prozent aller Schlafmittelvergiftungen die Spülflüssigkeit weniger als 1 cg und in 86 Prozent weniger als 10 cg d. h. die übliche therapeutische Dosis der Schlafmittel, wie Diallylnal, oder Allypropynal enthält.

Die zwischen Gifteinnahme und Magenspülung abgelaufene Zeit variierte wesentlich. Die Untersuchung der Beziehung zwischen der nach Einnahme des Giftes abgelaufenen Zeit in den Fällen, wo der Zeitpunkt der Giftzufuhr mit genügender Sicherheit

Tabelle 6.

Übersicht über die Menge der in der Spülflüssigkeit gefundenen Schlafmittel bei 71 Fällen von Schlafmittelvergiftung.

Im Spülwasser gefunden	Anzahl Fälle
0	38
0—0.01 g	7
0.01—0.1 g	17
0.1—0.26 g	8
> 0.5	2
Insgesamt	72

festgestellt werden konnte, und der Giftmenge in der Spülflüssigkeit ergab, dass nur in 2 Fällen, wo über 4 Stunden zwischen Gifteinnahme und Spülung vergangen waren, Gift in der Spülflüssigkeit nachgewiesen werden konnte, wenn von Mengen von 1 cg und weniger abgesehen wird. Im Falle Nr. 26 wurde nach 8 Stunden 0.02 g gefunden und im Falle Nr. 45 nach 4½ Stunden 0.26 g. In Fällen, wo der Zeitabstand zwischen Gifteinnahme und Spülung unter 4 Stunden war, zeigt eine Behandlung des Zahlenmaterials keine Korrelation zwischen der Menge des gefundenen Giftes und dem Zeitabstand.

Fall Nr. 10 illustriert wie geringe eine Bedeutung die Magenspülung häufig haben kann. Es handelt sich um eine Patientin, die ½ Stunde nach der Einnahme von 6 g Phenemal in Tablettenform selbst in das Hospital ging. Bei der etwas später vorgenommenen Magenspülung wurden nur 21 cg, d. h. etwa 3 Prozent der eingenommenen Menge gefunden. Dass die betreffende wirklich eine grosse Menge des betäubenden Mittels eingenommen hat, ist daraus ersichtlich, dass sie bei Beginn der Magenspülung getrübtetes Bewusstsein hatte und während der Spülung alsbald tief bewusstlos wurde.

Die Angaben über eingenommene Giftmengen, müssen natürlich mit grossem Vorbehalt bewertet werden (Spalte 2 Tabelle 4 und 5), wenn auch durch sorgfältiges Ausfragen versucht wurde, möglichst genaue Angaben zu erhalten. Eine Untersuchung der Zahlenwerte ergibt, dass eine Korrelation zwischen der Menge des eingenommenen Giftes und der in der Spülflüssigkeit gefundenen Giftmenge nicht vorhanden ist. Man könnte vielleicht vermuten, dass in den

Fällen, wo die Spülflüssigkeit kein Gift enthielt, und wo die eingenommene Menge nicht bekannt war, nur geringe Giftmengen eingenommen worden seien. Der schwere Vergiftungszustand, welchen die Mehrzahl der Patienten aufwiesen, deutet aber darauf hin, dass recht beträchtliche Dosen eingenommen sein werden müssen.

Eine Berechnung der in der Spülflüssigkeit gefundenen Giftmenge in Prozent der eingenommenen Menge ergibt für das vorliegende Material, *dass in der Mehrzahl der Fälle mit der Spülflüssigkeit nur einige wenige Prozent der eingenommenen Giftmenge entfernt worden sind.*

Nur in 5 Fällen von 80 wurde durch die Spülung mehr als 0.5 g entfernt und diese Fälle sollen im folgenden näher beschrieben werden.

I. Patient Nr. 31, 62 Jahre alte Frau, hat zu einem unbekannten Zeitpunkt vor der Einlieferung etwa 20 ml Hypnofentropfen = etwa 2 g Diemal + 2 g Allypropynal eingenommen. Bei der Einlieferung ist sie tief bewusstlos und ohne Reflexe. Die Respiration schnarchend, Puls und Gesichtsfarbe gut. Spülung und Kohleeingabe und Zufuhr von stimulierenden Mitteln wie üblich. Die Temperatur war einige Tage erhöht, dann aber normal. Am dritten Tage reagiert die Patientin etwas auf Ansprechen, befand sich dann aber wieder im Dämmerzustand. 78 Stunden nach der Einlieferung trat der Tod ein. Sektion: Bronchopneumonia dispers. et confluent. duplex.

In der Spülflüssigkeit vom Magen wurde 0.7061 g Barbitursäure gefunden. Im Mageninhalt, der bei der Sektion erhalten wurde, waren Barbitursäuren nicht nachweisbar, im Darminhalt fanden sich 0.0042 g.

II. Patient Nr. 53. Mann von 52 Jahren, der mehrere Stunden vor der Einlieferung ziemlich viel Alkohol getrunken hatte und etwa 2 Stunden vor der Einlieferung in das Hospital etwa 30 Dormintabletten = 4.5 g Äthylallylbarbitursäure eingenommen hatte. Bei der Einlieferung tief bewusstlos mit schnarchender Atmung. Hauttemperatur niedrig. Rektaltemperatur 35.6°. Spülung, Kohlezufuhr und Stimulantia in üblicher Weise. Reagierte am folgenden Tage etwas auf Ansprechen; dann wieder bewusstlos. 27 Stunden nach Einlieferung Exitus. Sektion: Degeneratio parenchym. organorum, Hypostasis pulm.; Oedema cerebri.

In der Magenspülflüssigkeit wurde 1.14 g, und im Darminhalt 0.08 g Barbitursäure gefunden.

III. Patient Nr. 30. Achtzehnjährige Frau, die 1 Stunde vor der Einlieferung 100 Codyltabletten = 25 g Phenazetin + 25 g Acetylsalizylsäure + 1 g Codeinphosphat eingenommen hat. Etwa $\frac{1}{2}$ Stunde später Erbrechen. Bei der Einlieferung ist die Patientin im Dämmerzustand und

leicht zyanotisch. Spülung in gewöhnlicher Weise mit 10 Liter Wasser. Nach beendigter Spülung wieder Erbrechen, und man bemerkt in dem Erbrochenen ein weiss gefärbtes Pulver. Daher wurde Apomorphinhydrochlorid (0.7 cg subkutan) injiziert, welches weiteres Erbrechen bedingte. Das Erbrochene wurde bedauerlicher Weise nicht analysiert. Eingabe von carbo medicinalis und übliche Behandlung. Am folgenden Morgen keine Bewusstseinstrübung mehr und in jeder Hinsicht normales Verhalten.

In der *Magenspülflüssigkeit* wurde insgesamt 1.44 g Phenazetin und Acethylsalizylsäure gefunden.

IV. Patient Nr. 72. Neunzehnjährige Frau, die etwa 1½ Stunde vor der Einlieferung 100 Chininpillen = 10 g Chininsulfat genommen hatte. Bei Einlieferung ist die Patientin verwirrt, klagt über Ohrensausen und Flimmern vor den Augen. Magenspülung und Kohleeingiessung wie üblich. Am folgenden Tag noch mässige Symptome von Seiten der Augen und Ohren, sonst normales Befinden.

In der *Magenspülflüssigkeit* wurde insgesamt 1.24 g Chinin gefunden.

V. Patient Nr. 80, neunzehnjähriger Mann der 3½ Stunde vor der Einlieferung 50 Chininpillen = 5 g Chininsulfat eingenommen hat. Erbrechen vor und während der Einlieferung. Der Patient ist nicht bewusstlos, hat Symptome von Seiten der Ohren; Magenspülung wie gewöhnlich.

In der *Magenspülflüssigkeit* wurde 0.61 g Chinin gefunden.

Von den angeführten Fällen waren zwei Barbitursäurevergiftungen. Was der Grund dafür sein kann, dass in diesen beiden Fällen so verhältnismässig grosse Mengen durch die Spülung entfernt wurden, wissen wir nicht. Aber wenn auch die durch die Spülung herausgeholtten Mengen im Vergleich zu den sonst bei der Spülung gefundenen Mengen ungewöhnlich gross sind, machen sie nicht mehr als 18 bzw. 25 Prozent der eingenommenen Menge aus, und *die Entfernung dieser Giftmenge durch die Magenspülung hätte nicht den Tod der Patienten verhindern können.*

Bei dem dritten Patient, der 50 g Phenazetin + Acethylsalizylsäure eingenommen hatte, wurde durch die Spülung 1.44 g, d. h. 3 Prozent des eingenommenen Giftstoffes beseitigt. In diesem Falle muss jedoch berücksichtigt werden, dass möglicherweise ein wesentlicher Teil der eingenommenen Giftmenge durch das Erbrechen vor der Spülung entfernt worden war. Auch hier kann der Magenspülung keine Bedeutung für den Zustand des Patienten zugeschrieben werden. Im übrigen sei darauf hingewiesen, dass in zwei anderen Fällen, wo auch Antipyretika eingenommen worden waren, nichts oder praktisch nichts in der Spülflüssigkeit vorhanden gewesen ist.

Bei dem vierten Patienten, der 10 g Chininsulfat eingenommen hatte, wurde bei der Spülung 1.24 g = 12 Prozent der eingenommenen Menge entfernt. Bei dem fünften Patienten wurden ebenfalls 12 Prozent einer eingenommenen Chininmenge von 5 g entfernt.

Die Verteilung des Giftes in den verschiedenen Teilen der Spülflüssigkeit.

Der Zweck der Analyse der einzelnen Spülflüssigkeitsportionen war zu untersuchen, mit einer wie grossen Flüssigkeitsmenge gespült werden muss, um zu entfernen was entfernt werden kann. Wider Erwarten fanden wir nur in sehr wenigen Fällen überhaupt nennenswerte Giftmengen in der Spülflüssigkeit, und das Material zur Beantwortung dieser Frage ist daher nicht gross. In Tabelle 7 ist das Material in dieser Hinsicht für 5 Fälle zusammengestellt, in denen durch die Spülflüssigkeit über 0.5 g beseitigt wurde.

Tabelle 7.

Verteilung des Giftes in den verschiedenen Fraktionen der Spülflüssigkeit nach Eingicssung von jeweils 1, 1, 2, 3 und 3 Litern.

Nr.	Gift	Durch Spülung entfernt gramm	in % der insgesamt durch Spülung entfernten Menge in				
			1. Fraktion	2.	3.	4.	5.
53	Aethylallylbarbitursäure	1.14	52	14	17	11	6
31	Somnifentropfen	0.71	18	11	22	39	10
30	Codyltabletten	1.44	83	6	5	3	3
72	Chinin	1.24	3	3	9	22	63
80	Chinin	0.61	55	16	6	2	1
<i>Mittelwert</i>			48	10	12	15	17

Tabelle 7 zeigt, dass in der Spülflüssigkeit nach Eingicssung von 1 Liter (der ersten Portion) im Mittel etwa die Hälfte der bei der Spülung mit 10 Litern insgesamt entfernten Giftmenge vorhanden ist. Die Ergebnisse variieren jedoch wesentlich in den verschiedenen Fällen. Im Falle Nr. 72 (Chinin) wurde nur 3 Prozent in der ersten Portion der Spülflüssigkeit gefunden, und 63

Prozent der gesamten heraufgeholtten Menge war in der fünften und letzten Portion vorhanden.

Für die Bewertung der Analysenresultate ist von Bedeutung, dass es im Durchschnitt nur gelang etwa 75 Prozent (im Mittel 7.6 Liter der eingegossenen 10 Liter) wieder heraufzuholen. Die übrige Menge (etwa 2.4 Liter) muss also im Magen-Darmkanal zurückgeblieben sein. Die Messung jeder einzelnen herausgeholtten Portion hat ergeben, dass der prozentische Verlust des eingegossenen Wassers in allen Portionen durchschnittlich gleich gross war.

4. Magenspülung bei Hunden mit abgebundenem Pylorus.

Wie im folgenden näher erörtert wird, besteht die Möglichkeit, dass der Transport von nicht unwesentlichen Giftmengen durch die Spülflüssigkeit in den Darm die Ursache für die Beseitigung von den nur sehr kleinen Giftmengen durch die Spülflüssigkeit ist. Um die Wirkung einer Magenspülung unter den bestmöglichen Bedingungen zu untersuchen, wurden Versuche an zwei Hunden mit unterbundenem Pylorus angestellt.

Technik:

Versuchstiere: Hunde. In Chloroformnarkose wurden die Tiere laparotomiert und der Pylorus unterbunden. Unmittelbar darauf wurde durch eine Magensonde 100 ml einer 2 prozentigen Lösung Allypropynal (durch eine aequivalente Menge Natriumhydroxyd in Lösung gebracht) in den Magen eingeführt. Fünf Minuten später wurde der Magen in der üblichen Weise mit einem Liter Wasser gespült und unmittelbar darauf mit einem weiteren Liter Wasser, welches 5 g carbo medicinalis enthielt.

Das Tier wurde dann mit Chloroform getötet und der an der Cardia unterbundene Magen herausgenommen. Der Magen wurde dann eröffnet, und der Inhalt so vollständig wie möglich entleert. Mengenbestimmungen des Allypropynal erfolgten 1. in der Magenspülflüssigkeit, 2. in der herausgeholtten Kohlesuspension, 3. in dem nach dem Tode im Magen vorhandenen Mageninhalt und 4. im Magen selbst. Die Analysen wurden nach der auf Seite 489 erwähnten Methode vorgenommen.

Ergebnisse:

Es wurden zwei Versuche angestellt. In einem Versuch war der Magen vor Beginn des Versuches leer, in dem anderen gefüllt.

Tabelle 8.

Versuch 1. Hund, Gewicht etwa 20 kg. 2 g Allypropynal wurden in 100 ml Lösung in den Magen eingeführt. Der Pylorus war abgebunden. Vor der Operation Fütterung des Hundes mit Graubrot.

Spülung mit	Bei der Magen- ausheberung erhaltene Flüssigkeit	Allypropynal gefunden	
		in Gramm	im Prozent d. eingegebene Menge
1000 ml Wasser	700 ml	0.610	30.5 %
1000 ml Kohlesuspension	1150 ml	0.430	21.5 %
Mageninhalt; Gewicht 300 g		0.167	8.4 %
Magen ; Gewicht 400 g		0.305	15.3 %
<i>Insgesamt</i>		1,512	75.7 %

Tabelle 9.

Versuch 2. Hund Gewicht etwa 10 kg. In den *leeren Magen* wurde 2 g Allypropynal in 100 ml Lösung eingeführt. Der Pylorus war abgebunden.

Spülung mit	Bei der Magen- ausheberung erhaltene Flüssigkeit	Allypropynal gefunden	
		in Gramm	im Prozent d. eingegebene Menge
1000 ml Wasser	1070 ml	1.190	59.5 %
1000 ml Kohlesuspension	925 ml	0.072	3.6 %
Mageninhalt; Gewicht 250 g		0.141	7.1 %
Magen; Gewicht 235 g		0.204	10.2 %
<i>Insgesamt</i>		1.607	80.4 %

Die Versuche ergeben, dass durch Spülung eines am Pylorus abgebundenen Magens beträchtliche Mengen der im Magen vorhandenen Barbitursäure entfernt werden können. In dem Versuch mit gefülltem Magen wurde mit 1 Liter Wasser etwa 30 Prozent und mit dem zweiten Liter etwa 22 Prozent, im ganzen 52 Prozent entfernt. Bei dem Versuch mit zuvor geleertem Magen wurde mit dem ersten Liter 60 Prozent und mit dem nächsten Liter nur 3—4 Prozent, d. h. insgesamt 63 Prozent entfernt. (Auf

die Bedeutung der Kohle soll in dieser Arbeit nicht eingegangen werden). Aber selbst unter den günstigsten Bedingungen (abgebundener Pylorus und leerer Magen), kann die Spülung mit 2 Litern nicht alles Gift entfernen. Mindestens 20 Prozent bleiben im Magen zurück. Es sei bemerkt, dass die Extraktion von Barbitursäuren besonders vom Organ selbst und von dem Mageninhalt mit Nahrung, in geringem Grade aber auch von der Spülflüssigkeit nicht mit 100 prozentiger Ausbeute vorgenommen werden kann. Die angegebenen Werte können daher nur als weitgehende Annäherung an die richtigen Werte aufgefasst werden.

5. Magenspülung mit Röntgenkontrastmittel bei schlafmittelvergifteten Personen.

Mit dem Fortschreiten unserer Untersuchungen stieg unser Misstrauen, dass ein nicht unwesentlicher Teil der Spülflüssigkeit schnell in den Darmkanal gelangen kann. Um hierüber genauere Aufschlüsse zu erhalten, wurden bei drei mit Schlafmitteln vergifteten Patienten mässigen Grades Magenspülungen mit 10×1 Liter Bariumsulfatsuspension unter stetiger röntgenologischer Kontrolle vorgenommen. Die Spülung erfolgte sonst ganz wie in den übrigen Fällen. Während der Spülung selbst, die gewöhnlich 15—20 Minuten dauerte, wurden mehrere Bilder aufgenommen, sowie ein Bild nach Abschluss der Spülung. Die auf diese Art behandelten Patienten mussten ausgewählt werden, da weder ganz leicht vergiftete Patienten, noch tief bewusstlose und stark mitgenommene Patienten für diese Versuche geeignet waren. Ein grösseres Material als die erwähnten drei Fälle konnte bisher nicht beschafft werden. Die Spülung wurde mit einer Suspension von 400 g »Neo-Bar« in 10 Liter Wasser vorgenommen und die untersuchten Fälle seien kurz angeführt.

A. Patient Nr. 87. Frau von 23 Jahren, die 5—6 Stunden vor der Einlieferung 0.8 g Phenemal genommen hat. Bei der Einlieferung verwirrt und im Dämmerzustand, kann geweckt aber nicht zum antworten gebracht werden. Während der Spülung wurden drei Röntgenbilder aufgenommen, und nach Abschluss der Spülung wurde die in Abbildung 1 wiedergegebene Röntgenaufnahme gemacht. Überlebt die Vergiftung.

Die Röntgenuntersuchung zeigt einen bei Beginn und zum Schluss der



Abb. 1. Röntgenbild vom Falle A, Patient Nr. 87. Patient in liegender Stellung.

Spülung etwas atonischen Magen. Nach der Spülung sind grosse Teile des Dünndarmes mit Kontraststoff gefüllt, auch der Magen enthält etwas Baryt.

B. Patient Nr. 88. Frau von 27 Jahren. Hat 38 Stunden vor der Einlieferung 2.7 bis 2.8 g Allypropynal genommen und seither geschlafen. Bei der Einlieferung und während der Spülung im Dämmerzustand, kann gerade ihren Namen nennen, aber sonst ohne Kontakt mit der Umwelt. Überlebt die Vergiftung.

Die Röntgenuntersuchung zeigt, dass Kontrastmittel nach der Spülung in grosser Ausstreckung in den Dünndarm gelangt ist. Schon ganz zu Beginn der Spülung sieht man, wie der Darm sich vom Magen her füllt (Abb. 2). Nach Abschluss der Spülung bleibt ein Teil der Spülflüssigkeit im Magen zurück (Abb. 3).



Abb. 2. Röntgenbild vom Fall B Patient Nr. 88. Aufnahme zu Beginn der Spülung. Patient liegend.

C. Patient Nr. 98. Mann von 51 Jahren. Hat eine Reihe von »weissen Schlafmittelttabletten« genommen. Bei der Einlieferung verwirrt und im Dämmerzustand-Allgemeinzustand gut.

Die Röntgenuntersuchung zeigt, dass nach Abschluss der Magenspülung beträchtliche Mengen des Kontrastmittels in den Dünndarmschlingen vorhanden sind die den grössten Teil des Abdomens bedecken. Möglicherweise ist ein Teil des Kontrastmittels bis in das Coecum gekommen (Abb. 4).

Die vorgenommenen Untersuchungen zeigen, dass die Spülflüssigkeit bei den untersuchten Patienten sehr schnell in den Dünndarm dringt. Diese Beobachtung deckt sich völlig mit den täg-



Abb. 3. Röntgenbild nach Abschluss der Magenspülung vom Fall B. Patient Nr. 88. (Patient in Vertikalstellung).

lichen Erfahrungen jeder Röntgenklinik, die sich mit den Untersuchungen des Verdauungskanalns nach Eingabe von Barytbrei oder ähnlichem beschäftigt.

6. Lungenmikroskopien.

Bei Obduktion von an Schlafmittelvergiftung gestorbenen Patienten, die mit carbo medicinalis behandelt worden sind, findet sich eine deutliche Schwärzung der Schleimhäute in den Bronchien, die durch Kohle bedingt ist. (Mündliche Mitteilung von Professor, Dr. med. Engelbreth Holm, Pathologisches Institut der Universität und von Prosektor, Dr. med. Willy Munck, Gerichtsmedizinisches

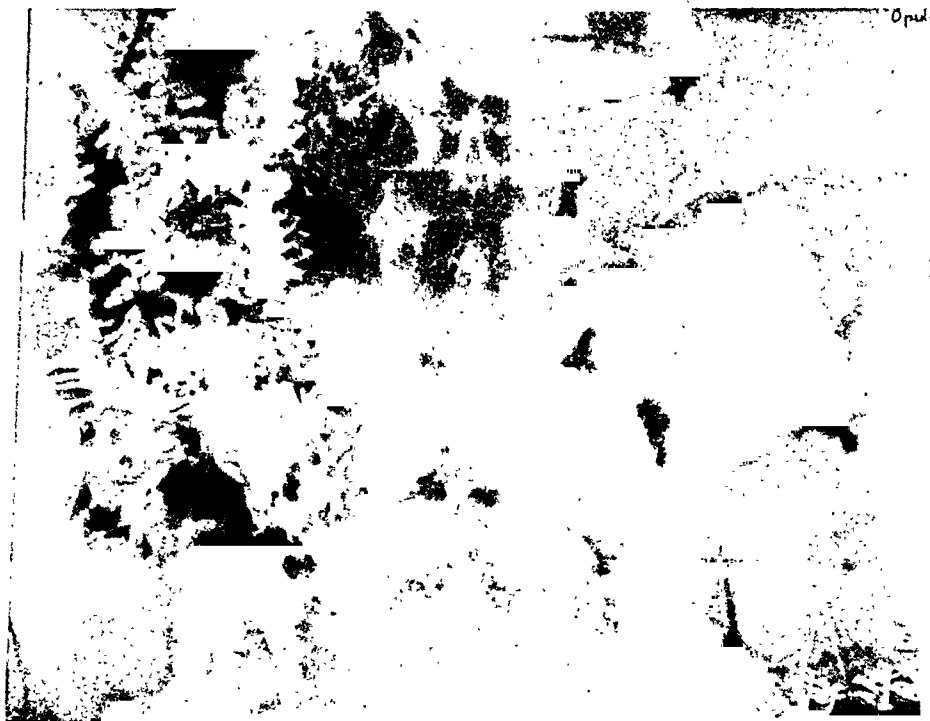


Abb. 4. Vom Falle C, Patient Nr. 98. Unmittelbar nach Abschluss der Magenspülung mit Kontrastmittel aufgenommen. Patient in liegender Stellung.



Abb. 5. Mikrophotographie der Lunge mit Kohlepartikeln, die frei in den mit Eiter gefüllten Alveolen liegen.

Institut der Universität.) Bei der Sektion von 9 nacheinander folgender Fällen von Schlafmittelvergiftung wurden Stücke der basalen Lungenabschnitte zur mikroskopischen Untersuchung herausgenommen. Bei 8 von 9 Patienten fanden sich frei in den Alveolen liegende Kohleteilchen (Abb. 5). Diese Kohlepartikel waren deutlich von dem in der Städterlunge normal vorhandenen Kohlenstaub zu unterscheiden. Die Spülung war in diesen Fällen nicht besonders schwierig.

Man muss annehmen, dass diese in den Alveolen gefundene Kohle durch Aspiration von Mageninhalt in die Lunge gelangt ist, da sämtlichen Patienten nach beendigter Magenspülung Kohle eingegeben wurde.

7. Besprechung der Versuchsergebnisse.

In Anbetracht des grossen Wertes, der gewöhnlich auf die Magenspülung bei Behandlung akuter Vergiftungen gelegt wird, haben unsere Untersuchungen zu dem überraschenden Ergebnis geführt, dass in der überwiegenden Mehrzahl der untersuchten Fälle nur ganz wenige Prozent oder häufig auch gar nichts der eingenommenen Giftmenge durch Spülung mit 10 Liter Wasser entfernt wird. Es besteht wohl kaum Grund anzunehmen, dass die Spülung in einem der hier vorliegenden Fälle therapeutischen Wert gehabt hat.

Da für die meisten Fälle Angaben über die eingenommene Giftmenge vorliegen, oder das klinische Bild einer schweren Vergiftung vorhanden war, können die in der Spülflüssigkeit gefundenen, kleinen Giftmengen nicht mit der Annahme erklärt werden, dass der Patient nur kleine Giftmengen eingenommen hat. Zur Erklärung der vorliegenden Versuchsergebnisse gibt es mehrere Möglichkeiten:

a) *Das Gift hat zum grössten Teil den Magen verlassen bevor die Spülung stattgefunden hat.* Wenn zwischen Gifteinnahme und Spülung längere Zeit vergangen ist, ist es leicht verständlich, dass im Spülwasser kein Gift gefunden wird. Unsere Untersuchungen haben ergeben, dass wenn über 4 Stunden vergangen ist bevor die Spülung erfolgt nur ganz ausnahmsweise nennenswerte Giftmengen in der Spülflüssigkeit vorhanden sind.

Aber auch in solchen Fällen, wo die Spülung kurz nach der Gifteinnahme vorgenommen wurde, haben wir bedeutungslose Giftmengen in der Spülflüssigkeit gefunden.

Man konnte es eigentlich von vorneherein als wahrscheinlich betrachten, dass der grösste Teil der eingenommenen Giftstoffe den Magen schnell verlässt, da die Giftstoffe, soweit es sich um Selbstmordversuche handelt, fast immer auf den leeren Magen eingenommen werden, wie es in den vorliegenden Fällen der Fall gewesen ist; (die Spülflüssigkeit ist ohne Nahrungsbestandteile gewesen), und wie es die sonstigen Erfahrungen der gerichtsschemischen Untersuchungen im pharmakologischen Institut auch gezeigt haben. Wie schnell eingenommene Giftstoffe (in Form von Tabletten) den Magen verlassen können, ist aus Tabelle 3 klar ersichtlich, die zeigt, dass bei im Laufe von einer Stunde an Strychninvergiftung gestorbenen Menschen die grösste Menge einer gleichzeitig mit dem Strychnin eingenommenen Eisenmenge bereits den Magen verlassen hat.

b) *Die Spülflüssigkeit befördert das Gift in den Darm.* Durch Messung der heraufgeholtten Menge Spülflüssigkeit ergibt sich unmittelbar, dass ein Teil der in den Magen eingeführten Spülflüssigkeit im Verdauungskanal bleibt. Von 10 Litern bleiben im Mittel 2.4 Liter zurück. Es ist unwahrscheinlich, dass eine so grosse Menge der Spülflüssigkeit im Magen zurückgelassen wird, und man muss annehmen, dass ein Teil der Spülflüssigkeit direkt in den Dünndarm gelangt. Versuche mit Spülung von mit Schlafmittelvergifteten Personen mit einer Röntgenkontrastflüssigkeit haben eindeutig gezeigt, dass während der Spülung Flüssigkeit in den Dünndarm evtl. bis zum Cöcum gelangt. In Versuchen mit Magenspülung bei Hunden mit *abgebundenem Pylorus*, wurde gefunden, dass die Spülung recht wirkungsvoll war, da durch Spülung mit 1—2 Litern 50—60 Prozent der im Magen vorhandenen Giftmenge entfernt werden konnte. *Wenn wir also bei unseren Untersuchungen der Spülflüssigkeit von vergifteten Personen nur so kleine Mengen finden, muss dieses bedeuten, dass entweder das Gift vor der Spülung den Magen schnell verlassen hat, oder dass das Gift den Magen durch den Pylorus mit einem Teil der Spülflüssigkeit verlassen hat, oder aber dass beide Möglichkeiten zutreffen.* Da die Spülung eine gewisse, nicht ganz kurze Zeit beansprucht, können Tabletten oder schwer lösliche Gifte durch die Spülung schneller

aufgelöst und dann schneller resorbiert werden als wenn die Spülung nicht vorgenommen worden wäre (vgl. Starkenstein, Rost und Pohl, 1929). Der zuvor erwähnte Fall Nr. 10, wo der Patient während der Spülung ziemlich plötzlich bewusstlos wurde, könnte durch die Annahme einer durch die Spülung bedingten, beschleunigten Resorption des Giftstoffes erklärt werden.

In unseren Untersuchungen des Mageninhaltes von an Schlafmittelvergiftung gestorbenen Personen, bei denen keine Magenspülung vorgenommen worden war, wurde in einigen Fällen wesentliche Giftmengen im Mageninhalt gefunden, obwohl 10—12 Stunden zwischen der Gifteinnahme und dem Eintritt des Todes vergangen waren. Diese Resultate stehen in scheinbarem Widerspruch zu den Untersuchungen der Spülflüssigkeit, aber der Widerspruch kann durch die Annahme erklärt werden, dass in einigen unserer Fälle, wo die Magenspülung vorgenommen wurde, zwar grosse Mengen des Giftes im Magen gewesen sind, dass diese aber zum grössten Teil durch die Spülflüssigkeit in den Darm befördert worden sind.

c) Adsorption des Giftes an die Magenschleimhaut.

Es besteht die Möglichkeit, dass gewisse Gifte im Magen so kräftig von der Magenschleimhaut adsorbiert werden, dass eine Spülung mit Wasser nicht im Stande ist die an die Schleimhaut adsorbierten Gifte zu entfernen. Diese Möglichkeit besteht bei Vergiftungen mit Schwermetallen und wurde für Sublimat von Dingemans und Laquer (1925) nachgewiesen. Im letztgenannten Falle war es möglich durch eine Spülung mit Kohlesuspension das Sublimat von der Schleimhaut zu entfernen, da die Adsorptionsaffinität zwischen Sublimat und Kohle grösser ist als zwischen Sublimat und den Schleimhäuten. Bei den hier untersuchten Giften (und in der Mehrzahl der Vergiftungen überhaupt) kann aber Adsorption an die Schleimhäute nicht von wesentlicher Bedeutung sein.

8. Die Bedeutung der Magenspülung bei akuten Vergiftungen; Vorschlag für eine rationelle Behandlung der akuten Vergiftungen.

Während wir glauben durch die vorliegenden Untersuchungen gezeigt zu haben, dass die Magenspülung bei Schlafmittelvergiftungen keinen oder nur äusserst geringen therapeutischen Wert hat, ist unser

Vergiftungsmaterial anderer Art zu klein, dass die gleiche sichere Schlussfolgerung auch für diese Fälle berechtigt ist, obwohl wir der Auffassung sind, dass unsere Resultate darauf hindeuten, dass die Magenspülung auch bei der Mehrzahl dieser Fälle ohne wesentliche Bedeutung gewesen ist.

Wie zuvor erwähnt, besteht in den toxikologischen Handbüchern Einigkeit darüber, der Magenspülung einen dominierenden Platz bei der Behandlung von akuten Vergiftungen einzuräumen. Starkenstein, Rost und Pohl (1929) äussern Zweifel hierüber und nennen die Behandlung mit Kohle an erster Stelle. Auch die Zeitschriftenliteratur ist über diese Frage nur sehr spärlich. Einzelne Untersucher raten bei bewusstlosen Patienten wegen der Gefahr einer Aspiration in die Lungen (Helpern, 1939) von der Magenspülung ganz ab, andere verlangen dass die Spülung so vorgenommen wird, dass Aspiration in die Lungen ganz verhindert wird (Marriott, 1933; Fantus, 1934; Volpitto, 1939). Während Volpitto (1939) glaubt, dass eine Spülung vorgenommen werden sollet, gleichgültig wie lange Zeit vergangen ist, meint Sack (1936) dass die Spülung nur dann Bedeutung hat, wenn sie kurze Zeit nach der Einnahme des Giftes vorgenommen wird. Eine nähere Beweisführung für diese verschiedenen Anschauungen fehlt vollkommen.

Die Frage der Bedeutung der Magenspülung hängt im wesentlichen Grade davon ab, ob die vergifteten Personen bewusstlos sind oder nicht.

Vergiftungen mit Bewusstlosigkeit: Wie schon mehrfach erwähnt, zeigen unsere Untersuchungen dass man nicht erwarten kann durch die Magenspülung, selbst wenn sie kurze Zeit nach Einnahme des Giftes erfolgt, wesentliche Mengen des Giftes zu entfernen. In Übereinstimmung mit mehreren Untersuchern sind wir der Auffassung, dass die Magenspülung bei bewusstlosen Personen eine ernsthafte Gefahr bedeutet (*«A stomach wash-out of an unconscious patient, whose cough reflex is absent, may be lethal»*, Marriott, 1933).

Die klinische Beobachtung auf der psychiatrischen Abteilung des Bispebjerg Hospitals hat folgendes ergeben: In einer Reihe von Fällen, hat man den Eindruck, dass die Patienten im Anschluss an die Magenspülung einen schlechteren Zustand zeigten. Wenn die Patienten nicht tief bewusstlos sind, haben sie während und unmittelbar nach der Spülung wiederholtes Erbrechen. Im Anschluss hieran, kann die Respiration unregelmässig werden und die

Patienten werden zyanotisch, als ob Spülflüssigkeit in die Lungen aspiriert worden wäre. Einzelne Male trat Kollaps auf, sodass die Spülung schleunigst abgebrochen werden musste. Unmittelbar nach Eingiessung der Kohlesuspension haben viele Patienten erbrochen, und man erhielt den Eindruck dass die langdauernde Reizung der Magenschleimhaut durch die Magenspülung mit grossen Wassermengen die grosse Brechbereitschaft bedingt hat. Man versuchte das Erbrechen mit einer kleinen Dosis Atropin zu verhindern, aber ohne Erfolg. Magenspülung des Patienten mit herabhängendem Kopf (Körper horizontal) wurde versucht, musste aber aufgegeben werden, da diese Stellung in der Regel die Respiration verschlechterte und die Zyanose verstärkte.

Spülung in Trendelenburgscher Lagerung (Beckenhochlagerung) wurde in den hier vorliegenden Fällen nicht angewandt.

Bekanntlich ist die Todesursache in den meisten Fällen von Schlafmittelvergiftung Aspirationspneumonie und nur in wenigen Ausnahmefällen eine Lähmung des Vasomotoren- und Atemzentrums. Da alle Patienten mit *carbo medicinalis* behandelt waren, haben wir in Übereinstimmung hiermit Kohle in den Lungenalveolen gefunden. Wieweit die vorausgegangene, energische Magenspülung durch Reizung der Magenschleimhaut und Steigerung der Brechreflexe die Gefahr einer Aspiration in die Lungen erhöht hat, kann aber nicht entschieden werden. Als weiteres Gefahrenmoment kommt die zuvor erwähnte Beschleunigung der Giftresorption in Betracht.

Wir glauben daher schliessen zu müssen, dass bei bewusstlosen, vergifteten Patienten die Magenspülung eine wesentliche Gefahr ohne Vorteile bedeutet, und in solchen Fällen muss die Magenspülung, wenn nicht spezielle Massnahmen vorgenommen werden (s.unten), als kontraindiziert angesehen werden.

In Fällen von Vergiftungen, wo der Patient wach ist, sind die Hustenreflexe erhalten und die Gefahr einer Aspirationspneumonie ist dann nur sehr gering. Die Magenspülung mit Wasser bietet bei solchen Patienten (ebenso wie bei Bewusstlosen) die Gefahr einer Beschleunigung der Giftresorption, entweder dadurch dass ein Teil des Giftes während der Spülung in den Darm befördert wird, oder weil Tabletten und schwerlösliche Gifte schneller in Lösung gebracht werden.

Andererseits kann die Magenspülung zweifellos gelegentlich

auch wesentliche Giftmengen aus dem Magen entfernen. Da die Gefahr einer Aspirationspneumonie bei diesen Patienten minimal ist, und da man der Gefahr einer beschleunigten Giftresorption durch Spülung mit Kohlesuspension entgegen wirken kann, *muss eine Magenspülung mit Kohlesuspension oder eine auf andere Weise vorgenommene Leerung des Magens beim wachen Patienten als indiziert angesehen werden.*

Für die Seite der Behandlung akuter Vergiftungen die soweit wie möglich eine Resorption des eingenommenen Giftes verhindern will, (vgl. Einleitung S. 478) sei im folgenden ein Vorschlag angeführt, wobei Vergiftungen mit Säuren, Basen und anderen ätzenden Stoffen nicht berücksichtigt werden.

Bewusstlose Patienten: Da man bei Behandlung jedes einzelnen Vergiftungsfalles, besonders wenn das Gift auf den vollen Magen eingenommen worden ist, immer mit der, wenn auch nur seltenen Möglichkeit des Vorhandenseins grosser Giftmengen im Magen rechnen muss (vgl. Fall Nr. 3 Tabelle 4), muss man versuchen den Magen zu leeren. Spülung mit Wasser wie es jetzt meist üblich ist, ist unserer Auffassung nach nicht indiziert. Wir möchten die Einführung einer Magensonde vorschlagen, durch die, durch Aspiration, eine Leerung des Magens versucht wird. (Zur Aspiration scheint die »Clyso-Pumpe« geeignet zu sein; zwischen Gummiballon und Magensonde, wird eine Flasche zum Auffangen von Mageninhalt eingesetzt¹. Wenn der Magen leer ist, werden ohne andere Behandlung carbo medicinalis (10 g Kohlegranulat oder mehr auf 200—300 ml Wasser) und Magnesiumsulfat als Abführmittel (15—20 g, die dem Wasser zugesetzt werden) eingenommen. Die Flüssigkeitsmenge darf nicht zu gross sein, um nicht die Neigung zum Erbrechen zu steigern. Die Bedeutung der Adsorptionstherapie mit Kohle ist seit langem anerkannt und erneut durch eine längere Untersuchungsreihe, die später von Harrestrup Andersen aus dem pharmakologischen Institut veröffentlicht wird, festgestellt worden, weswegen hier nicht näher auf diese eingegangen wird.

Wenn bei der Aspiration grössere Mengen Mageninhalt herausgeholt werden, kann man eventuell den Magen mit 1—2 Litern einer Suspension von carbo medicinalis in Wasser (etwa 10 g per

¹ Mageninhalt sollte immer für eine eventuelle, spätere chemische Untersuchung aufgehoben werden.

Liter) spülen. Der Kohlezusatz bedingt, dass ein möglicherweise im Magen vorhandenes Gift sofort von der Kohle gebunden wird¹; sollte es dann in den Darm transportiert werden, wird die Resorption des Giftes jedenfalls verzögert. Die Spülung wird mit der zuvor erwähnten Eingiessung von Kohle und Magnesiumsulfat beendet.

Bei dem bewusslosen Patienten sollte unserer Auffassung nach die Spülung nur auf einem Untersuchungstisch vorgenommen werden, wo der Patient mit gesenktem Oberkörper angebracht werden kann (Trendelenburgsche Lagerung) evtl. unter Anwendung irgend einer Sauganordnung im Rachen des Patienten, von der Art der von Zahnärzten zum Aufsaugen von Speichel benutzten Anordnung. Hierdurch wird die Gefahr der Aspiration von Spülflüssigkeit in die Lungen wesentlich herabgesetzt. Ebensolche Forderung für die Ausführung der Spülungen wurden auch von Marriott (1933) und von Fantus (1934) gestellt.

Nicht bewusslose Patienten: Auch beim wachen Patienten soll so schnell wie möglich versucht werden, den Magen durch Aspiration zu leeren, evtl. mit folgender Anwendung einer Magenspülung, wie sie im vorhergehenden beschrieben worden ist. Bei diesen Patienten, deren Hustenreflex erhalten ist, kann eine Spülung in der üblichen Art und Weise vorgenommen werden. Bei vergifteten *nicht bewusslosen Patienten* sollte unserer Meinung nach in Erwägung gezogen werden, ob die *subkutane Injektion von Apomorphin zur Hervorrufung von Erbrechen nicht wieder als Hilfsmittel bei der Behandlung benutzt werden soll*. Der im Augenblick für Brechmittel übliche Kommentar, dass »Brechmittel den Magen weniger vollkommen leeren als eine Spülung es tue« (vgl. fast alle Hand- und Lehrbücher), muss wahrscheinlich revidiert werden. Entsprechende Untersuchungen, wie die vorliegenden, über die Wirkung und Anwendung von Brechmitteln, sind äusserst wünschenswert.

Obwohl es ausserhalb unseres eigentlichen Themas liegt, seien einige Bemerkungen über die Nachbehandlung narkotischer Vergiftungen hinzugefügt. Diese muss soweit möglich verhindern, dass Mageninhalt in die Lungen gelangen kann. Es sei daher auf einige Vorkehrungen hingewiesen, die soweit uns bekannt hier-

¹ Starke Säuren und Basen und einzelne andere, von Kohle nicht adsorbierten Giften werden in diesem Zusammenhang nicht berücksichtigt.

zulande nicht allgemein benutzt werden, deren Wichtigkeit von Fantus (1934) und Volpitto (1939) hervorgehoben wird, und die auch uns von wesentlicher Bedeutung zu sein scheinen. *Das Fussende des Bettes des Patienten soll erheblich gehoben werden (etwa 20 Grad);* wenn notwendig, werden die Füße des Patienten am Fussende des Bettes befestigt. Der Kopf wird auf die Seite gelegt und wenn Erbrechen oder starke Speichelsekretion vorhanden ist *ein ständiges Aussaugen von Mund und Rachen mit einem »Speichelsauger« vorgenommen.* Eine dauernde Überwachung des Patienten ist erforderlich, um die Luftwege (evtl. durch Aussaugen) frei zu halten und um häufig den Patienten im Bett zu wenden.

Zusammenfassung.

1. Bei 55 an akuten Schlafmittelvergiftung gestorbenen Patienten, bei denen keine Magenspülung vorgenommen worden war, wurde die im Magen vorhandene Giftmenge bestimmt. In der Mehrzahl der Fälle finden sich nur sehr geringe Mengen des Giftes im Magen.

2. Bei 80 Patienten mit sicher diagnostizierten, akuten Vergiftungen, die durch Spülung des Magens mit 10 Liter Wasser behandelt worden sind, enthält die Spülflüssigkeit in der grossen Mehrzahl der Fälle nur einige wenige Prozent der eingenommenen Giftmenge. In keinem der beobachteten Fälle konnte der Magenspülung ein therapeutischer Wert zugeschrieben werden.

3. Bei Spülung von Mägen mit abgebundenem Pylorus (Hundeversuche) können mit 1—2 Liter Flüssigkeit etwa 50—60 Prozent der im Magen vorhandenen Giftmenge entfernt werden.

4. Von 10 Litern eingegossener Spülflüssigkeit werden im Mittel nur 7.6 Liter wieder gewonnen; die übrige Menge wird in den Darm befördert.

5. Bei Magenspülung schlafmittelvergifteter Personen mit einer Röntgenkontrast gebenden Flüssigkeit ergibt die direkte Beobachtung, dass während der Spülung selbst Flüssigkeit in den Dünndarm, evtl. bis zum Coecum herabdrängt.

6. Es wird angenommen, dass das Auftreten von nur sehr kleinen Giftmengen in der Magenspülflüssigkeit zum Teil darauf beruht, dass das eingenommene Gift sehr schnell in den Darm befördert wird, und zum Teil dadurch bedingt wird, dass die im

Magen vorhandene Giftmenge in mehr oder weniger grossem Umfange zusammen mit der Spülflüssigkeit in den Darm transportiert wird. Die Adsorption von Gift an die Magenschleimhaut ist nur bei Vergiftungen mit Schwermetallen und einzelnen anderen Stoffen von Bedeutung.

7. In Vorschlägen für die Behandlung von akuten Vergiftungen wird hervorgehoben, dass Magenspülung bei bewusstlosen Patienten grosse Gefahren enthält ohne Vorteile zu bieten. Die Magenspülung sollte im allgemeinen durch die Magenleerung durch Aspiration ersetzt werden. Sofern eine Magenspülung erwünscht ist, sollte diese mit einer Suspension von carbo medicinalis in Wasser und höchstens 1—2 Liter Flüssigkeit vorgenommen werden.

Bei nicht bewusstlosen Patienten sollte Apomorphin als Brechmittel möglicherweise anstatt Magenspülung gebraucht werden. Genauere Erfahrungen hierüber fehlen doch.

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A Contribution to the knowledge of the Prognosis of Epilepsy.

By

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In general, the conception that epilepsy has a predominantly bad prognosis undoubtedly prevails among laics as well as among doctors. This view was shared by several earlier authors, as, for instance, Esquirol (11), Delasiauve (11) and Georget (11), who were exceedingly pessimistic as regards the chances of recovery. However, in the middle of the 19th century a turning-point set in. Trousseau (6) was able to produce 20 cases out of 150 who were restored to health. Furthermore, Herpin (6) revealed 20 healed cases out of 48. Towards the end of the century, well-known authors in the field of epileptic research, such as Gowers (4), Féré (3) and Binswanger (2), were of the opinion that epilepsy was curable. Thus, according to Féré, the prognosis assumes a serious nature in proportion to the frequency of the attacks, the number of stigmata of degeneracy, and the degree of the hereditary affliction of the diseased person. Moreover, Féré believed that, in the majority of cases, children recovered from epilepsy. The possibility of such a cure also with regard to adults he attributed to their »successful power of resisting the epileptogenic influence of the irritant to which they had been exposed». He had himself observed four cases of healing without treatment in individuals who had been taken ill after the age of forty years.

During the present century, several investigations have been performed concerning the prognosis of epilepsy. An illumination, to some degree, of this subject has also been the purpose of the present work.

In 1901, Habermaas (6) published an after-examination of 937 epileptics, 863 of whom had been nursed at an institution and 74 of whom had been subjected to polyclinical treatment. Cases that had been free from epileptic manifestations for a period of five years were regarded by him as healed. He found that 10.3 per cent disclosed healed epilepsy with maintained ability to work. In 0.6 per cent epilepsy was cured but the patients were not able to work owing to dementia. 21 per cent of the total number of patients were quite fit for work, 30 per cent suffered from decreased working ability, while 49 per cent were unable to work. As a rule, Habermaas considered those cases most favourable where no direct cause was ascertainable, where spasms had not occurred in infancy, where, in addition, no »pathological changes of the brain» could be determined, and, finally, where the patient concerned did not show any signs of dementia or merely insignificant ones.

Volland (11) was able to get hold of 138 patients out of 245 who had been discharged as »healed» from an epileptic institution. The surprisingly high figure of 83 of the cases, viz, 60.1 per cent, were still free from attacks after a period of observation of 6—20 years.

At an after-examination of 111 polyclinically treated patients, Stern (10) found that 24.3 per cent had been relieved of seizures for ten years. However, Stern does not wish to define these cases as »healed». Instead, he prefers to describe them as »mild cases». He emphasizes, no doubt justifiably, the fact that only mild and benign cases are met with at an after-examination. — 38.7 per cent of the patients had died. 14.4 per cent of the rest still suffered from epilepsy or had only been free from attacks for two years. 22.5 per cent received care at a mental hospital.

In 1927, Irene Guttman (5) performed an investigation of all the epileptics under Kraepelin's observation at the Munich clinic, during the years 1904—1922. She was in a position to obtain information regarding 279 surviving males and 157 females, i. e. 436 patients in all. It was found that 59.9 per cent of the males and 59.2 per cent of the females, or, in sum, 59.6 per cent, were fit for work. 42 patients, viz. 9.6 per cent, included among those fit for work, were

defined as completely »sound». Since the year 1904, 39.3 per cent of the males and 38.7 per cent of the females had died. In a comparison between the death causes, it was seen that epilepsy was fatal, particularly often in younger age groups.

Owing to the varying nature of the materials, a comparison between the figures of the different statistics would hardly be of any value. In one of his tables, Habermaas distinguishes between »cortical» and »typical» epilepsy. Otherwise, however, he gives no particulars regarding the composition of the material. Volland includes, inter alia, traumata and encephalitis, among the etiological factors. In nearly all »healed» cases, Stern discovered some cause for the first seizure and, partly, also for the following ones. In these cases, toxic, infectious and traumatic factors were decisive.

The significance of *heredity* with regard to the prognosis of epilepsy has been subjected to much discussion. According to Gowers, heredity might be expected to exert an unfavourable influence on the prognosis. Nevertheless, he had a strong impression that heredity often played a part in cases where treatment had a remarkable effect. On the other hand, as mentioned above, Féré took a more pessimistic view of the matter. Habermaas did not consider that »hereditary affliction» exerted the unfavourable influence that was almost »generally ascribed to it». 37.4 ± 5.3 per cent of the healed epileptics were hereditarily afflicted in Volland's material. The difference, viz. 62.6 ± 5.3 per cent, between the other healed cases and the abovementioned group is statistically significant (the figures are calculated by the author of the present paper). However, Volland does not give an explanation of what he means by »hereditary affliction». As stated above, among Stern's patients, exogenous factors were decisive as regards the »healed cases», while the hereditary factor was of great importance concerning the »not healed» ones. In approximately 60 per cent of the last-mentioned cases, epilepsy was ascertained in the genealogical tree or in the siblings. Moreover, epilepsy occurred in the children, a fact, however, which also took place among the »healed» cases. — Hoffman (7) is of the opinion that, if »hereditary degeneration» exists to a fair degree of certainty, »hereditary regeneration» must, also, be possible. In support of this contention regarding epilepsy, he draws attention to the genealogical tree, published by Oberholzer (8), which »gives a striking picture of the gradual decrease of the patho-

logical symptoms». Oberholzer studied an epileptic family through four generations and found »regeneration» in the latter generations. »Regeneration» was apparent, partly through the appearance of spontaneous healing and, partly, through the replacement of convulsive attacks by mild forms of epilepsy (i. e. vertigo and fainting fits). — Redlich (9) was the originator of the term *oligoepilepsy*, serving as a definition of cases subjected to isolated fits, or sometimes only one. He lays stress on one particular group among the oligo-epileptics, viz, relatives of epileptics, a father or mother or siblings, who have related that they themselves suffered from isolated epileptic attacks, in their childhood or in their youth, which have not returned later. However, Redlich considers it as only »partially accurate» to describe hereditary affliction as favourable. — In Sweden, Antoni (1) has stressed the occurrence of spontaneously healed epilepsy in two generations, without destruction of personality, and with maintained fitness for work and sociability.

The present investigations.

The material of the present investigation comprises patients with the diagnosis »Epilepsia» subjected to treatment at the Nerve Clinic of Serafimerlasarettet, during the years 1931—1938. Forms were sent to these patients with the following requests: that they give an account of their epileptic symptoms, before and after their detention at the Nerve Clinic, their medicine, their present occupation, whether they had been continually fit for work after their stay at the Clinic and, finally, the possible existence of relatives suffering from epilepsy. 174 of the answers obtained, i. e. approximately 40 per cent of the dispatched forms, were suitable for analysis.

18 of the 174 patients stated that cranial trauma with unconsciousness had preceded the epileptic manifestations. In 17 cases, the interval between the trauma and the epileptic manifestations varied between that of a few months and thirty years. In 1 case the patient had an attack on the same day that she was exposed to a cranial trauma. After that she was not subjected to fits for five years, when she again suffered a relapse. — Epilepsy appeared in 4 patients in connection with an infectious disease, i. e. 2 cases with Spanish influenza, 1 case during morbilli and another one together

with an acute encephalitis. In one instance the disease made its appearance ten years after parotitic encephalitis. — One patient had an attack while lying ill with »albuminuria» (Nephritis ?). However, the next attack did not turn up until after nine years. — In the remaining 150 cases, no etiological factor whatsoever existed. Nevertheless, the statement that trauma or infection was the cause of epilepsy cannot be made with certainty in any of the above-mentioned 24 cases.

5 patients revealed unilateral facialis paresis. One was a prey to paresis since birth. Another had a »distorted face» for many years and two patients had suffered from acute encephalitis (Encephalography: in 3 cases the encephalograms were normal, in 1 case the lateral ventricles were dilated, and in another one the ventricular system was not filled up.) — 4 patients disclosed spastic hemiparesis. (Encephalography: the encephalogram was normal in 1 case, in another patient one of the lateral ventricles was dilated, and in yet another one septum pellucidum had deviated and one of the lateral ventricles was dilated. The ventricular system of one patient was not filled up.) — Finally, Babinski was positive on one side in 1 patient. (Encephalography: the ventricular system was not filled up.) — Otherwise, no definite pathological-neurological symptoms occurred in the material.

In 69 of the 174 cases encephalography had either not been performed, or the ventricular system was not at all, or only partially, filled up. The encephalograms of the other 105 patients revealed the following facts: in 42 cases dilatation of one or both lateral ventricles, or an abundance of air on the convexity, or dilated sulci, in 11 cases deviation of septum pellucidum, in 4 cases a deformation of the ventricular system, in 1 case dislocation of this system, and in another instance calcification at the apex of one of the anterior cornua. Finally, in 56 cases the encephalograms were normal.

Table I.

	Non-hereditary cases	Hereditary cases	Total
Males	78	12	90
Females	70	14	84
Total	148	26	174

Table II.

Year of detention at the Nerve Clinic.	Number of cases.	Cases free from attacks for 3 years. + cases now subjected to attacks	Free from attacks for 3 years and more.	Altogether fit for work.	Not quite fit for work.	Considerable decrease in ability to work.	Deaths.
1931	3	3 = 100 ± 0 %			2 = 66.6 ± 27.2 %		1 = 33.3 ± 27.2 %
1932	8	4 = 50 ± 17.7 %	4 = 50 ± 17.7 %	5 = 62.5 ± 17.1 %	1 = 12.5 ± 11.7 %	2 = 25 ± 15.3 %	
1933	14	11 = 78.6 ± 11 %	3 = 21.4 ± 11 %	10 = 71.4 ± 12.1 %	1 = 7.1 ± 6.9 %	2 = 14.2 ± 9.3 %	1 = 7.1 ± 6.9 %
1934	15	12 = 80 ± 10.3 %	3 = 20 ± 10.3 %	11 = 73.3 ± 11.4 %	2 = 13.3 ± 8.8 %	2 = 13.3 ± 8.8 %	
1935	12	7 = 58.3 ± 14.2 %	5 = 41.7 ± 14.2 %	9 = 75 ± 12.5 %	1 = 8.3 ± 8 %	2 = 16.7 ± 9.6 %	
1936	26	21 = 80.8 ± 7.7 %	5 = 19.2 ± 7.7 %	15 = 57.7 ± 9.7 %	8 = 30.8 ± 9.1 %	3 = 11.5 ± 6.3 %	
1937	29	23 = 79.4 ± 7.5 %	6 = 20.6 ± 7.5 %	18 = 62.1 ± 9 %	8 = 27.6 ± 8.3 %	2 = 6.9 ± 4.7 %	1 = 3.4 ± 3.4 %
1938	41	35 = 85.4 ± 5.5 %	6 = 14.6 ± 5.5 %	22 = 53.7 ± 7.8 %	7 = 17.1 ± 5.9 %	12 = 29.2 ± 7.1 %	
Hereditary cases.	148	116 = 78.4 ± 3.4 %	32 = 21.6 ± 3.4 %	90 = 60.8 ± 4 %	30 = 20.3 ± 3.3 %	25 = 16.9 ± 3.1 %	3 = 2 ± 1.2 %
	26	20 = 76.9 ± 8.3 %	6 = 23.1 ± 8.3 %	14 = 53.9 ± 9.8 %	8 = 30.8 ± 9.1 %	4 = 15.3 ± 7.1 %	

Table III.

	Cases free from attacks for 3 years + cases now subjected to attacks.	Free from attacks for 3 years and more.
Males	69 = 76.7 ± 4.5 %	21 = 23.3 ± 4.5 %
Females	67 = 79.8 ± 4.4 %	17 = 20.2 ± 4.4 %
Total	136 = 78.2 ± 3.1 %	38 = 21.8 ± 3.1 %

The composition of the material with regard to sex distribution and heredity will be seen in Table 1. In the hereditary case, epilepsy was noticed in the father, or the mother, or the siblings, or the children, or the siblings of the parents, or the siblings of the grandparents. Furthermore, the disease was also recorded in the cousins, or in the cousins of parents, or the cousins of grandparents. To my knowledge the epilepsy of the relatives was not of a symptomatic nature. In the non-hereditary cases, either no definite data regarding heredity were presented, or the answer in the form was »No case heard of in the family».

As regards medicine, several patients have constantly taken the prescription administered at the Nerve Clinic, others have acquired new prescriptions from another doctor, and some have not taken any medicine at all, if free from attacks for some time. Many confessed to occasional carelessness in taking their medicine.

78.4 ± 3.4 per cent of the non-hereditary cases were still subject to seizures or enjoyed relief for less than three years, the corresponding figure for hereditary cases being 76.9 ± 8.3 per cent. The figure for the entire material in this group equals 78.2 ± 3.1 per cent. 21.6 ± 3.4 per cent of the non-hereditary cases and 23.1 ± 8.3 per cent of the hereditary ones were free from attacks for

Table IV.

	Altogether fit for work.	Not quite fit for work.	Considerable decrease in ability to work.	Deaths.
Males	51 = 56.7 ± 5.2 %	19 = 21.1 ± 4.3 %	19 = 21.1 ± 4.3 %	1 = 1.1 ± 1.1 %
Females	53 = 63.1 ± 5.3 %	19 = 22.6 ± 4.6 %	10 = 11.9 ± 3.5 %	2 = 2.4 ± 1.7 %
Total	104 = 59.8 ± 3.7 %	38 = 21.8 ± 3.1 %	29 = 16.7 ± 2.8 %	3 = 1.7 ± 0.9 %

Table V.

	Cases free from attacks for 3 years. and more with full ability to work.	Cases free from attacks for 3 years. and more but not altogether fit for work.
Hereditary cases	6 = 23.1 ± 8.3 %	0
Non-hereditary cases.	28 = 18.9 ± 3.2 %	4 = 2.7 ± 1.3 %
Total	34 = 19.5 ± 3 %	4 = 2.3 ± 1.1 %

three years or more, i. e. altogether 21.8 ± 3.1 per cent. There is no difference as regards sex.

Patients reporting that they had been compelled to absent themselves from work certain days have been included in the group »Not quite fit for work». In addition to those who had not been able to work at all, persons admitted to an epileptic institution have been referred to the group »Not fit for work». — 60.8 ± 4.0 per cent of the non-hereditary cases were quite able to work, and, correspondingly, 53.9 ± 9.8 per cent of the hereditary ones, i. e. comprising in all 59.8 ± 3.7 per cent. No statistical difference is ascertainable between hereditary and non-hereditary cases, or between men and women. 4 patients out of 38, viz. 2.3 ± 1.1 per cent, who had been free from attacks for three years or more, declared that they were not entirely fit for work.

Three of 174 patients had died. The death cause was not set down. In addition, six patients who were not included in the material, owing to incompletely filled in or blank forms, had died.

With regard to three patients, who had been questioned, epilepsy was found, after some time, to be due to a cerebral tumour. These cases were not included in the statistical calculations.

Six patients, four of whom underwent seizures at the time of the investigation, mentioned that some relative of theirs had been the victim of epilepsy of a transient nature.

The present material is, of course, too restricted and the time of observation too brief to permit an accurate judgement of the number of epileptics remaining free from attacks and utterly fit for work. The fits may reappear, as Binswanger and Redlich have pointed out, after a very long interval. Other figures might, perhaps, have been obtained, if answers had been received from all the patients inter-

rogated. It is, possible, naturally, that an increased dose of medicine, or an exchange, or addition of another medicine might lead to complete relief in the case of many epileptics who are, at present, suffering from attacks. Then, as a matter of course, the number of those fit for work would be greater. However, the fact may be emphasized that the percentage figures of those altogether fit for work reveal relatively big conformity as between the different year groups (cp. Table II). Moreover, the figure of the total material of the same category, viz, 59.8 ± 3.7 per cent, conforms with that of Irene Guttman, viz, 59.6 per cent.

Summary.

After a survey of previous investigations of the prognosis of epilepsy, the present author has submitted the results obtained at an after-examination of 174 patients, with the diagnosis »Epilepsia», subjected to treatment at the Nerve Clinic of Serafimerlasarettet, during the years 1931—1938. — 21.8 ± 3.1 per cent were found to have been free from attacks for 3 years or more, 78.2 ± 3.1 per cent being free from attacks for less than 3 years. Patients completely fit for work comprised 59.8 ± 3.7 per cent, those not altogether fit for work equalling 21.8 ± 3.1 per cent. The ability to work was stated to have been considerably decreased in 16.7 ± 2.8 per cent of the cases. Finally, 1.7 ± 0.9 per cent of the patients had died. — No statistical difference was ascertainable between the hereditary and the non-hereditary cases as regards relief from attacks and the degree of fitness for work.

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Contribution to Our Knowledge of the Pathogenesis of Unilateral Exophthalmus.

Experiments with Blocking of the Stellate Ganglion.

By

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Exophthalmus can arise: a) from the ball of the eye being pressed forward passively by a process restricting the orbital space (inflammatory tissue; edema; tumour); b) by the ball being carried forward by contraction of non-striated musculature in the orbit; or c) by the combined action of these factors. The two latter possibilities have been greatly discussed, especially in connection with the genesis of exophthalmus in thyreotoxicosis, where one is easily tempted to assume the action of such a muscular contraction, brought about by a sympathetic factor. The problem, we think, has not yet been solved, however.

In certain cases, exophthalmus, as a symptom, may give rise to differential diagnostical difficulties, especially if it be unilateral. Such cases of unilateral exophthalmus are frequently difficult to explain, the possibility of the presence of a tumour being a factor which gives rise to uneasiness.

Starting from the fact that blocking of the stellate ganglion occasions enophthalmus (as one phenomenon in Horner's symptom-

complex), we have assumed that a blocking of the stellate ganglion on the same side as the exophthalmus might possibly cause the said symptom to diminish, if its origin is to be sought for in an irritation of the sympathetic nerves. As, from a theoretical point of view, such an irritation can hardly exist if a tumour is the cause of the exophthalmus, our experiments, from the very beginning, have aimed at attempting to contribute to differential diagnosis in cases of unilateral exophthalmus; *i. e.*, to elucidate whether their cause may be sympathicotonic, or tumoric.

Our material consists of three cases from the Medical Clinic of the Caroline Hospital, Stockholm.

Case 1: A woman, 30 years old, who got her left-sided exophthalmus eight months after operation for Graves' disease, after which it had continued for five months. She still displays some thyreotoxic symptoms (nervosity; perspirations).

Status: exophthalmus left (1 mm difference from the right eye); the upper eyelid retracted about 3 mm on gazing straight forward. — Skull and orbital X-ray negative. Relative metabolism: + 18 %.

9. 2. 1942: *Blocking of the left stellate ganglion (A.-R.)* with 10 cm³ 1 % etocain. After about 15 minutes, the diameter of the left pupil is 1 mm less than that of the right. No difference as regards the breadth of the rima oculi, nor in the exophthalmus (Dr. Olof Olson, Ophthalmological Clinic, Caroline Hospital).

11. 2. 42: *Renewed blocking of the left stellate ganglion (A.—R.)* gives exactly the same result (again examined by Dr. Olson).

The patient, later on, was attended to at the Neuro-Surgical Clinic of the Serafimer Hospital, without any further diagnostical results.

Case 2: A woman, 58 years old. In 1937, struck the right elbow. Since 1938, varying, reddened infiltration in lower part of right arm, attended by aching. Since the autumn of 1941, patient has grown somewhat thinner, perspired, lost hair, has felt nervous and uneasy. Rima oculi of right eye has gradually grown wider.

Status: Right-sided exophthalmus 3 to 4 mm in protrusion; slight enlargement of thyroid; lumbar puncture and skull X-ray negative; relative metabolism +24 %, + 20 %, + 19 %, + 3 % (diminishing values during treatment with bromide and barbiturics).

21. 2. 1942: *Blocking of the right stellate ganglion (A.—R.)* with about 4 cm³ 1 % etocain; there is at once obtained miosis (about 1 mm pupil difference, but no ptosis nor diminished exophthalmus) (Hanström, Ophlt. Clinic). In the evening, the arm ached more than usual.

Case 3: Man, 28 years of age who, in the autumn of 1938, had struck his head, and since had had headache in the right temple, which increased

during last year. From Aug. 1941, increasing rightsided exophthalmus. Latterly, somewhat more nervous. Perspirations.

Status: Right-sided exophthalmus (and a slight left-sided one, too). Protrusion difference about 3 mm (Olson). Moderate goitre. LP, skull X-ray and neurological examination negative. Relative metabolism: + 18 %, + 14 %.

6. 3. 42: *Blocking of the right stellate ganglion (A.—R.)*, with about 5 cm³ 1% etocain; there is obtained evident miosis, but no reliable effect on exophthalmus (Olson).

The patient was afterwards transferred to the Neurological Clinic of the Serafimer Hospital, where no further positive finds were made.

Discussion of the cases: All three cases have had unilateral exophthalmus for about half a year. In none has the investigation given any support for tumour-diagnosis, but, on the other hand, a number of symptoms speaking against it. At the same time, the increased relative metabolism has pointed to the possibility of a slight thyreotoxicosis. Special interest is attached to Case 1, where the exophthalmus developed after operation for Graves' disease (cf. Jensen: *Nord. Med.* 1939: III, p. 2466: postoperative exophthalmus of hypophyseogenetical origin?) Clinically, consequently, there is nothing to contradict the assumption that this slight thyreotoxicosis might be the cause of the unilateral exophthalmus.

In spite of this, the blocking of the stellate ganglion led to no diminished protrusion of the eye-ball (but to clearly evident miosis), although, theoretically, it might have been expected. Judging by the cases spoken of above, blocking of the stellate ganglion is probably valueless as a differential-diagnostical method in cases of exophthalmus. One may suppose that this negative result arises: a) because the theory of the excitation of the sympaticus, with attendant contraction of the non-striated musculature of the orbit, as the cause of exophthalmus, is erroneous — for we know that exophthalmus in Graves' disease does not disappear on sympathectomy; and, in *The Lancet*, 1939: 237, p. 1217, there is described by Brain a case of exophthalmus in Graves' disease in spite of sympathetic paresis of many years' duration; — or, b) that it is due to the condition in the orbit's being all too inveterate to allow of treatment (cf. all the operated cases of Graves' disease, where the exophthalmus disappears only slowly, or not at all).

Summary.

The authors have carried out blocking of the stellate ganglion in three cases of unilateral exophthalmus, probably of thyreotoxic origin, hoping thereby to contribute to the differential diagnosis, by distinguishing such exophthalmus from the exophthalmus caused by tumour.

The experiments proved negative: the exophthalmus did not diminish.

There is a short theoretical discussion of the cause of this negative result.

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The Electrocardiogram in Anterior Wall Infarction.¹

Further Studies on the QRS Changes in Precordial Leads.

By

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(Submitted for publication August 7, 1942).

In recent years our electrocardiographic knowledge of cardiac infarction has increased considerably through the employment of precordial leads. The typical changes in the extremity leads were established already a decade ago, and no essentially new facts have been added since, except for the entirely negative finding that the changes observed in cardiac infarction on employment of the extremity leads are quite uncharacteristic far more frequently than assumed before. This applies both to the acute infarction and to the fibrous infarction, but particularly to the latter. In the present paper, therefore, I shall limit myself to the question: What does the introduction of precordial leads mean to the electrocardiographic diagnosis of cardiac infarction?

In *posterior wall infarction* the extremity leads will most often show characteristic changes, while the precordial leads merely show changes in RS-T in the acute stage and are of no particular diagnostic value.

In *anterior wall infarction*, on the other hand, the changes in the extremity leads will often be slight and uncharacteristic, especially

¹ Read before the Danish Society of Internal Medicine, May 30, 1942.

in the subacute and chronic cases. Here the precordial leads show some very characteristic changes and are of great diagnostic importance.

In order to get an idea of how often the extremity leads fail diagnostically, I have analyzed the material of anterior wall infarction in which the localization and extent of the infarct was demonstrated on autopsy (Table 1).

Table 1.

Electrocardiographic Findings in 19 Cases of Anterior Wall Infarction examined post mortem.

Specific changes in	Extremity leads	Precordial leads
QRS.....	5 (26 %)	11 (58 %) + 5 (+26 %)
RS-T and/or T.....	8 (42 %)	14 (74 %)
QRS and/or RS-T and T..	8 (42 %)	16 (84 %)

The material comprises 19 cases of anterior wall infarction, recent and fibrous, examined post mortem. From Table 1 it will be noticed that in more than one-half of the cases the extremity leads showed no specific changes — by which we mean: a large Q_1 , small R_1 together with large S_2 and S_3 (Winternitz' Type I), negativity of the main deflection of the QRS complex in all 3 leads (Winternitz' Type II), elevation of RS- T_1 and depression of RS- T_3 , besides typical negative coronary T_1 . With precordial leads the specific changes were found far more frequently, namely: elevation of RS-T both in a parasternal derivation and an apical or typical negative coronary T in one or both precordial leads and an abnormal, initially negative, deflection in the QRS complex. In 5 additional cases the precordial leads showed suspect but not quite characteristic changes in QRS. Even though this material is not very large, it still conveys a strong impression of the insufficiency of the extremity leads in anterior wall infarction. Some examples are shown in Figs. 1, 2 and 4.

A (Fig. 1) shows an electrocardiogram taken 5 days after an acute attack of cardiac disease. There are elevation of RS-T in Leads II and III and a completely negative QRS complex in both of these leads — changes

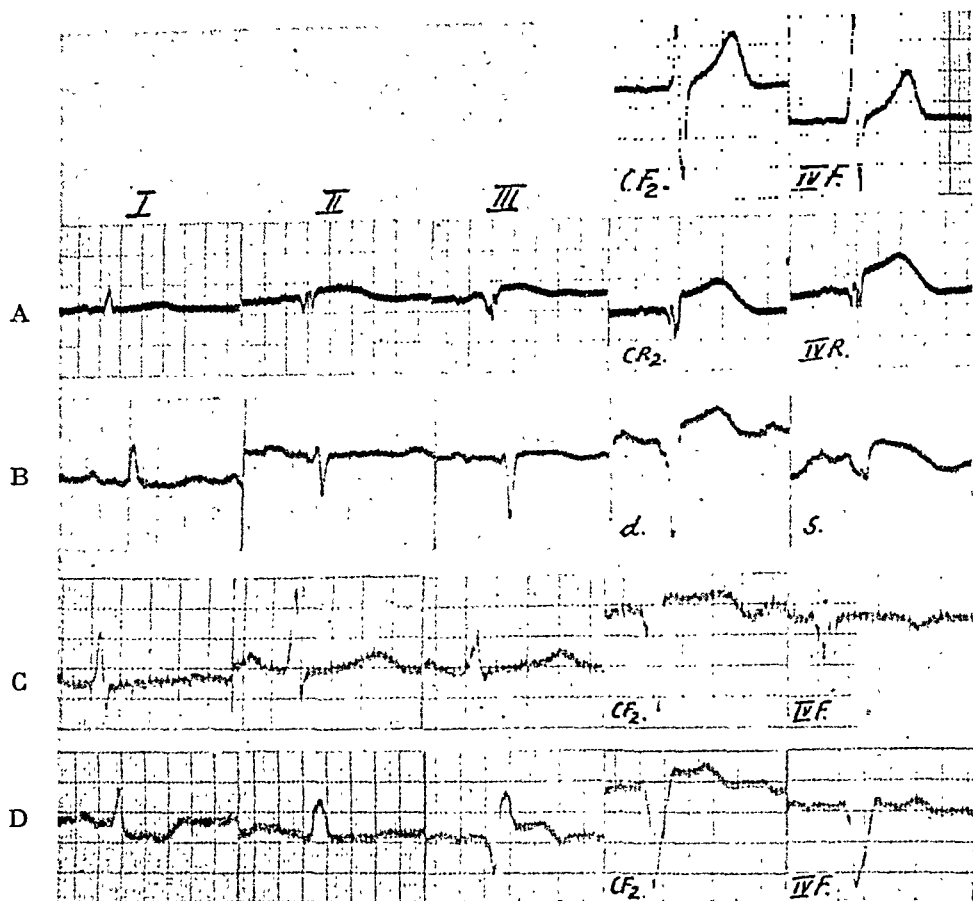


Fig. 1. Above, a normal, precordial electrocardiogram in CF_2 and IVF . A, B, C and D show tracings from 4 cases of anterior wall infarction. No sign of this lesion seen in the extremity leads; typical changes in the precordial leads. In all the tracings, 1 cm = 1 mV. (The distance between two horizontal lines is 0.5 cm.)

which, according to Durant, often signify the same as Q_2 and a large Q_3 . The findings in the extremity leads are therefore suggestive of acute posterior wall infarction, and there is no evidence of anterior wall infarction in these leads. The precordial leads show changes typical of anterior wall infarction, namely: elevation of RS-T and completely negative, notched QRS complex in both precordial leads. So in this case the precordial leads indicated the presence of an acute anterior wall infarction, and this diagnosis was verified on autopsy.

B shows an electrocardiogram from another case, taken 10 days after an acute attack of cardiac disease. The precordial leads show unspecific changes or perhaps a suggestion of posterior wall changes, whereas the precordial leads show very pronounced anterior wall changes. Autopsy revealed anterior wall infarction.

C shows the record of a man who was admitted in an unconscious state with hemiplegia. The extremity leads show merely a flat T_1 , but otherwise no abnormality. The precordial leads show very typical signs of anterior wall infarction. Autopsy revealed a fibrous anterior wall infarct (besides cerebral hemorrhage).

D shows a record taken a few hours after an acute attack of cardiac disease in a man. The extremity leads present the changes typical of posterior wall infarction. Both precordial leads show an almost completely negative QRS complex indicating anterior wall infarction. Autopsy revealed anterior wall + posterior wall infarction. In this case the precordial leads are a little atypical, showing a small initial positive wave. According to my experiences, this variation is most frequent just in the cases where the anterior wall infarction is combined with the presence of another infarct.

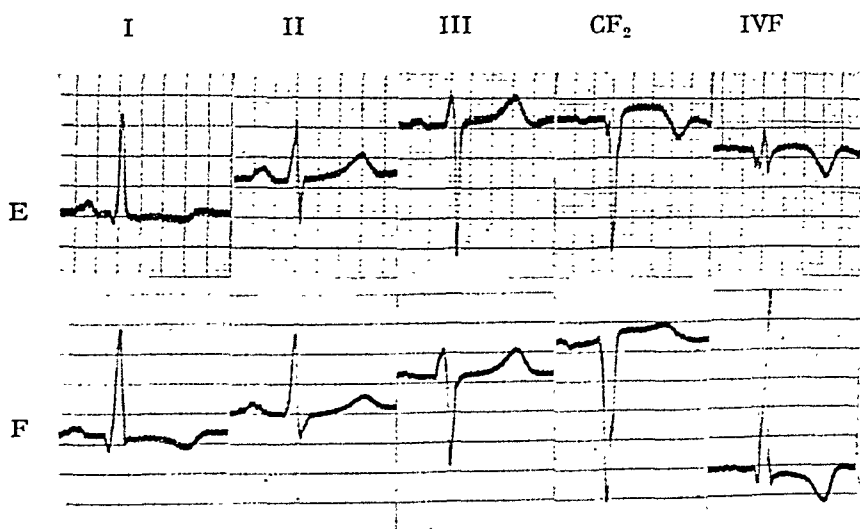


Fig. 2. E: Tracing from a patient with an anterior wall infarct of 8 months' standing. F: Tracing from a patient with hypertensive cardiac disease.

Finally I shall present a case that illustrates very plainly why the extremity leads easily may fail in anterior wall infarction (Fig. 2).

E shows an electrocardiogram of a patient with anterior wall infarction taken 8 months after onset; F shows an electrocardiogram of a patient with hypertensive cardiac disease without infarction. The records obtained with derivation from the extremities in the two cases are practically alike and show the common type of left-sided preponderance with negative T_1 and positive T_3 . As anterior wall infarction in the later stages gives a negative coronary T_1 and a positive coronary T_3 , which subsequently loses all its specific stamp, we will very often in chronic anterior wall in-

infarction obtain a tracing of the type here presented — the more so as typical QRS changes, as shown in Table 1, are found only in about one-fourth of the cases. It is quite impossible on such extremity electrocardiograms to make the differential diagnosis between fibrous anterior wall infarction and hypertensive heart lesion. On the other hand, it is easy to make the differential diagnosis on employment of precordial leads, which in anterior wall infarction give an elevated RS-T followed by an inverted T (in both precordial leads), besides typical QRS changes, whereas in cases of marked left-sided preponderance we find a diminished initial R wave in CF_2 , an increased R wave in IVF (in this case also a small normal Q wave), besides isolated inversion of T in IVF. The present instance shows distinct changes in RS-T and T in precordial leads (Fig. 2, E), but these changes are transitory — like the RS-T and T changes in the extremity leads, and hence we cannot reckon with their presence at a later stage of the lesion. The QRS changes, on the other hand, are stable and will often be the only specific changes in fibrous anterior wall infarction. I therefore look upon them as particularly important, and I have made them the subject of further investigation.

According to the previous view, the typical QRS changes in the precordial leads, irrespective of the derivation employed, consist in a diminution or, more frequently, complete disappearance of the R wave so that in the classical infarction curve the QRS complex is completely negative (such a curve is seen, for instance, in Fig. 3, J, Lead CF_2). On analysis of the tracings obtained with Leads CF_2 and IVF in 23 cases of anterior wall infarction I found the classical infarction curve to be present only in some of the cases. Other cases showed a different type of QRS complexes with a more or less preserved R wave preceded by an abnormal Q wave so that the QRS complex was notched, in some cases W-formed (as seen, for instance, in Fig. 3, J, Lead CF_4). As in other cases of infarction I found transitions between these two types, I had to subscribe to the view presented by Wilson and collaborators on the basis of animal experiments: that the typical QRS changes could not be characterized by the fact that the R wave disappears, but that it is the matter of a coincidence of two factors, namely, the appearance of a Q wave and the diminution, increasing to complete disappearance, of the R wave; the classical infarction curve is seen only in the special instance where the diminution of R is complete. The feature common

to all the infarction curves is the abnormal Q wave, which then has to be considered the most characteristic abnormality. This view of the QRS changes means an extension of the classical criteria, and after these extended criteria we shall be able to diagnose considerably more cases of cardiac infarction than after the classical conception.

On further investigation the structure of the QRS changes was found to become considerably clearer when a series of precordial derivations are employed, instead of limiting them to CF_2 and IVF.

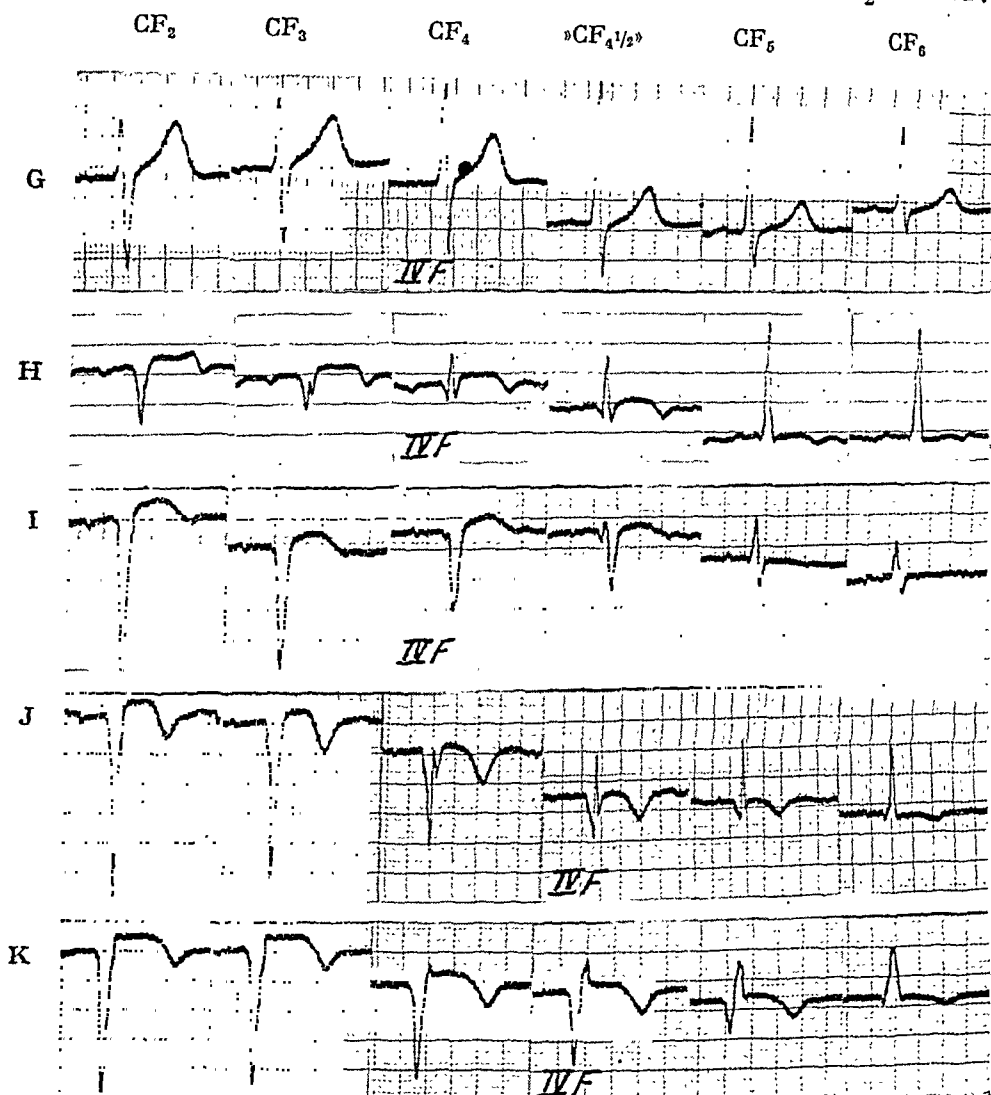


Fig. 3. G shows a series of normal precordial electrocardiograms. H, I, J and K shows the corresponding precordial tracings in 4 cases of anterior wall infarction.

Fig. 3 presents some electrocardiograms taken in this manner. G shows a series of normal precordial tracings in Leads CF_2 , CF_3 (midway between CF_2 and the medioclavicular line), CF_4 (medioclavicular line), » $CF_{4\frac{1}{2}}$ » (midway between CF_4 and CF_5), CF_5 (anterior axillary line) and CF_6 (medioaxillary line). H, I, J and K show tracings taken with the same derivations from 4 patients with anterior wall infarction. It will be noticed how the QRS complex changes quite gradually as the electrode is moved laterally. The most pronounced changes are found in CF_2 , and they decrease laterally, being quite inconspicuous or absent in the axilla. The connection between the classical and the split curves is plain, and so is the development of the R wave from notching of the classical curves. The changes are not equally pronounced in all cases. In some cases typical infarction curves are found in derivations even so far out to the side as from the anterior axillary line; in other cases they are not encountered laterally to the midclavicular line. I have seen other cases in which the tracings showed a normal QRS complex even in CF_4 .

These series show that there is no fundamental difference between the classical and the split or W-formed curves. Both are equally characteristic of anterior wall infarction. The series further prove that the new view of QRS changes is correct. In all 4 cases we find within a more or less limited area of the precordium the appearance of an abnormal, initially negative, deflection and a more or less pronounced diminution of the R wave. In particular, the last case (K) illustrates very plainly that it would be rather artificial to characterize the QRS changes by absence of the R wave.

The new conception of the QRS changes is of great practical value. Often the classical infarction curve is found only in the medial precordial leads, and then its diagnostic significance is uncertain because a marked preponderance of the left part gives diminution of the R wave or — though relatively seldom — complete absence of the R wave in the same derivations. So when we find a totally negative QRS complex in CF_2 , we have to make sure that it is an infarction curve and not a preponderance curve by the demonstration of an abnormally large Q wave in a more lateral precordial lead, preferably in IVF.¹

¹ The Q waves are considered abnormally large when in CF_2 and IVF they exceed respectively 2 and 3 mm and are larger, respectively, than $\frac{1}{4}$ and $\frac{1}{5}$ of the following R wave.

Naturally, then, the question suggests itself: Might it not be sufficient merely to employ Lead IVF — as has been suggested by the American and British Committee of Standardization? Yes, undoubtedly this would be sufficient in many cases. But, the QRS changes disappear rapidly on moving the electrode laterally to IVF and in some instances they are absent already in IVF, so that they would readily escape detection in some cases if only IVF was employed. The safest procedure is, therefore, to take the electrocardiograms both in CF₂ and IVF. These leads are sufficient in most cases, but it may be necessary sometimes also to employ the intermediate precordial leads.

In conclusion, I shall cite some cases that illustrate the employment of precordial leads after these principles in practice.

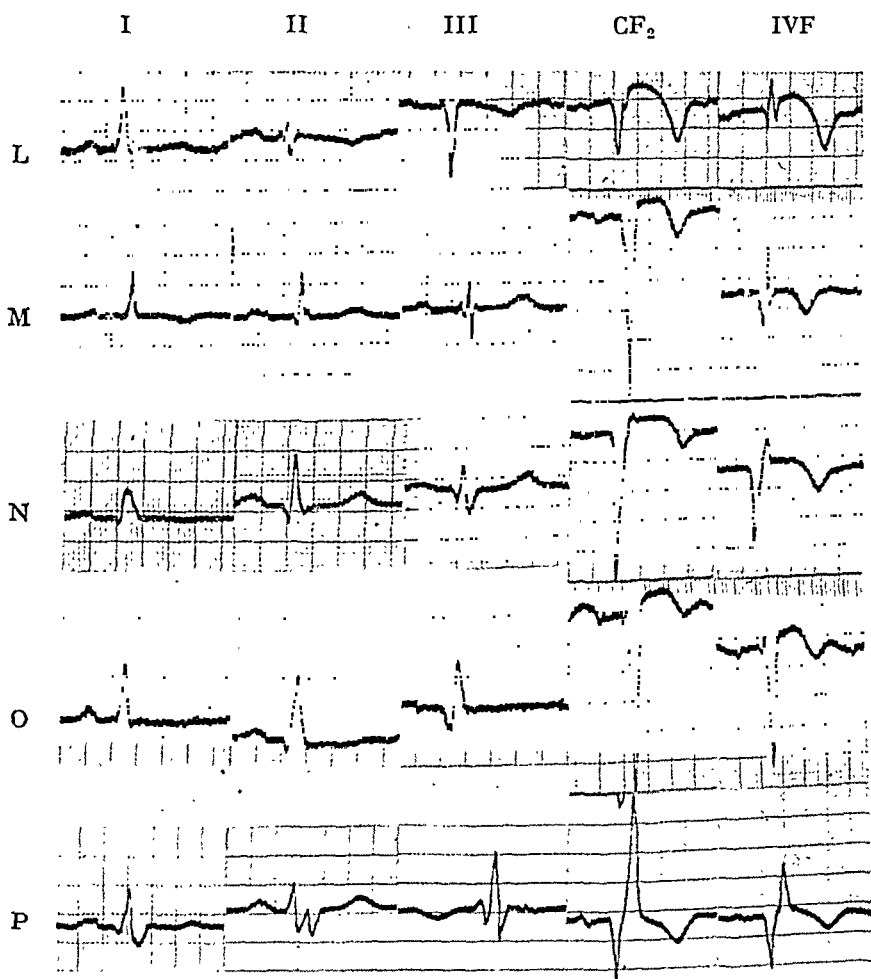


Fig. 4. Electrocardiograms from 5 cases of anterior wall infarction. The extremity leads show only doubtful signs of anterior wall infarction or none at all. The precordial leads show pronounced signs of this affection.

In Fig. 4, L shows an electrocardiogram taken 4 months after an attack of acute coronary occlusion. There is no sign of anterior wall infarction in the extremity leads. In CF_2 the QRS complex is completely negative, with a little notching. IVF shows that here we are dealing with infarction curves, as is also indicated by RS-T and T in the precordial leads.

M shows tracings from a patient with pulmonary tuberculosis, but without any severe cardiac complaints in the anamnesis. The changes in the extremity leads may be due to hypertrophy of the left ventricle and do not allow of a diagnosis of infarction. In CF_2 we see a completely negative QRS that may be due to anterior wall infarction or marked hypertrophy of the left ventricle. In IVF the abnormally large Q wave shows that here we meet with an instance of anterior wall infarction, as is also indicated by the T waves in the precordial leads.

N shows an electrocardiogram from a man 4 years after a typical attack of coronary occlusion with very typical anterior wall changes in the extremity leads. Now there are no definite signs of anterior wall infarction in the extremity leads, but unquestionable signs of such a lesion in the precordial leads. (Discussion quite as in Case M.)

O shows an electrocardiogram of a patient 4 weeks after a typical attack of coronary occlusion. No specific changes in RS-T and T in the extremity leads but presence of Q_2 and a large Q_3 , indicating posterior wall infarction. Both precordial leads show an almost completely negative QRS complex with slight notch, very typical of anterior wall infarction. Anterior + posterior wall infarction?

P shows an electrocardiogram from a patient taken 4 months after an acute attack of cardiac disease, accompanied by RS-T and T changes in the extremity leads typical of anterior wall infarction. Now the electrocardiograms show Wilson block, but no sign of anterior wall infarction in the extremity leads. Both precordial leads show abnormally large Q waves that can be due only to anterior wall infarction (besides inversion of the T wave in both precordial leads).

In this paper I have described only the *typical* electrocardiographic changes seen on employment of precordial leads in anterior wall infarction. In many cases of cardiac infarction the changes will deviate somewhat from the typical, but these cases do not detract from the great value of the precordial leads. A large clinical material will include so many cases in which the location of the infarct is atypical and cases of multiple infarcts that it would be quite unreasonable to expect that the electrocardiograms would follow an established scheme.

The introduction of precordial leads means that now we are able to diagnose many more instances of cardiac infarction than pre-

viously — in particular, it is possible now to diagnose also the relatively mild cases and to diagnose them long after the acute attack.

Through this, our conception of cardiac infarction has been altered considerably. Previously the lesion was taken to be relatively rare and very serious; now we know that it is very frequent and that its prognosis is better than assumed previously. Thus, a survival of 10—15 years is not infrequent.

Summary.

On the basis of an autopsy material, the writer shows that the extremity leads fail in more than one-half of the cases of clear-cut anterior wall infarction, and that the accuracy of the diagnosis improves considerably on additional employment of precordial leads.

Through further studies on the QRS changes in precordial leads in anterior wall infarction, the view of their structure as presented in a preceding paper is confirmed. Accordingly the greater importance is to be attached to the presence of an abnormal Q wave and, to a lesser extent, to a decrease in, or absence of, the R wave.

References.

For references to the literature concerning this question, see Vagn Mortensen: *Om elektrokardiografiske Forandringer ved Hjerteinfarkt*. København 1940. (With an summary in English.) — Vagn Mortensen: *Die elektrokardiographische Diagnose des Herzinfarkts*. *Archiv f. Kreislaufforschung* X, 27, 1942.

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Aggregations of cases of acute meningo-encephalomyelitis of unknown genesis.

By

HARALD SANDSTRÖM.

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During the last 20 years interest in the «non-purulent inflammatory conditions» in the central nervous system has increased considerably, and the literature in that field is extremely comprehensive and covers practically all countries. While in America research work has been mainly concentrated on certain morbid conditions of known etiologies, in a number of European countries aggregations of cases of meningo-encephalomyelitis of unknown geneses have been described. Interest in these questions was aroused chiefly by Wallgren's description of such cases in Gothenburg in 1922—24. In Sweden during recent years aggregations of similar cases have been described by Ljungström from the Hälsingborg district in 1930—31, by Bexelius from Gotland in 1935—36, and by Möller from Sollefteå in 1939. The disease has also been described by several other authors, but not in connection with any direct aggregation of cases. From Germany, Holland, Spain, England, Hungary, Turkey and the Scandinavian countries similar morbid conditions of unknown geneses appearing more or less epidemically have been described. In the following discussion, inflammatory conditions in the central nervous system appearing simultaneously with, or in connection with, any known epidemic infection disease, such as scarlatina, measles, mumps, etc. are left entirely out of account.

Whether acute meningo-encephalomyelitis cases of unknown genesis really have increased in number during the last few decades, it is difficult to decide, but it appears that the majority of authors consider that such is the case. The question will be dealt with more in detail in connection with the discussion on the relation to poliomyelitis.

Many attempts have been made to arrive at a clear and comprehensive classification of the inflammatory conditions in the central nervous system. In the majority of cases it is impossible strictly to distinguish meningitis cases from encephalitis and myelitis cases respectively. More or less pronounced symptoms from either the meninges, brain or spinal marrow, or possibly from two or three quarters at the same time, are met with in the majority of the »epidemics» which have been described.

Eckstein made the following classification in 1929:

1. Epidemic meningitis (encephalitis epidemica lethargica Economo).
2. Chronic encephalitis (post encephalitic condition).
3. Encephalitis epidemic of other genesis
 - a) acute encephalitis (Strümpels)
 - b) Australian X-encephalitis
 - c) St. Louis-encephalitis
 - d) Bern-encephalitis
 - e) Japanese B-encephalitis.
4. Sporadic encephalitis.
5. Para- and post-infectious encephalitis.
6. Postvaccinal encephalitis.

In American quarters several attempts at classification have been made. L. T. Webster distinguishes no less than 9 different forms of encephalitis with known etiologies: 1. Rabies-enc. 2. Poliomyelitis. 3. St. Louis-enc. 4. Japanese B-enc. 5. »Louping ill». 6. Australian X-enc. 7. »Equin» encephalomyelitis. 8. Lymphocytic choriomeningitis. 9. B. encephalitis. All these forms are transferable to animals. In this connection he mentions also herpes-encephalitis and Economo's encephalitis, but he points out at the same time that their etiology is not fully elucidated.

J. A. Toomey has made the following classification, which he himself does not claim to be exhaustive, but which is surveyable:

A. Encephalites secondary to or simultaneous with acute infections.

1. Morbilli, scarlatina, pertussis, parotitis, tbc, lues etc.
2. Hemorrhagic encephalitis.

B. Encephalites secondary to the consumption or injection of alcohol, arsenic, etc.

C. Encephalites associated with poisoning.

D. Encephalites, toxic neuropathia, encephalopathia not due to known infection diseases. Other synonyms: diffuse meningo-encephalomyelitis of unknown genesis, multiple neuritis, toxic neuronitis, dissociated encephalitis, aseptic meningitis, benignant lymphocytic meningitis. Possibly acute multiple sclerosis also belongs here.

E. Encephalites associated with disturbances in metabolism, e. g. uraemia, etc.

F. Encephalites associated with increased pressure in the brain, as in pachymeningitis, extradural abscess, fractures, etc.

G. Encephalites in connection with serum or vaccine treatments.

H. Encephalites caused by specific virus.

I. Diseases which simulate encephalitis, such as neurosis, purulent meningitis, acute chorea and vascular lesions in the brain.

This attempt at classification according to etiological principles is naturally imperfect, not least as regards the group »diffuse meningo-encephalites of unknown genesis», i. e. the morbid conditions, which will be dealt with below. In Sweden we have been content on the whole to distinguish between encephalitis resulting from or concomitant with infectious diseases, and encephalitis with an entirely unknown genesis.

Discussion on the subject of the genuine meningo-encephalomyelites (below abbreviated to men.enc.myel.) has mainly concerned itself with the identity with, connection with, or differential diagnosis from poliomyelitis (pol.myel), opinions differing considerably. Apart from the purely scientific interest, the question is of great importance both from purely practical nursing points of view, and also from the point of view of treatment. Eckstein and Schneider consider that it is a question of a meningeal form of encephalitis epidemica, but for the majority of other authors the problem has been whether they are dealing with a disease sui generis or an abortive or meningeal form of pol-myel. In the discussion a con-

fusing number of arguments and counter-arguments have been advanced, and sometimes the conclusions appear to be drawn more from a so-called general impression, or from a tendency, noticeable even from the beginning of the discussion, to stress certain details at the expense of others, which perhaps do not fit in so well with the author's conclusions, than from purely scientific considerations. That the question is difficult of solution is also shown by the fact that in a number of cases the same author has changed his opinion from one year to another.

Here in Sweden, Wallgren, Antoni etc. appear at the present time to adopt the point of view that it is a matter of abortive forms of pol. myel., although Wallgren will not deny that there are cases of aseptic meningitis *sui generis*, possibly appearing epidemically. With the support of epidemiological factors, Rolf Bergman considers that the cases of serous meningitis which appear epidemically are abortive pol. myel. cases. Möller discusses the differential diagnosis exhaustively and considers that in the cases he has described it is chiefly a matter of disseminated encephalomyelitis cases appearing epidemically, which resemble pol. myel. especially in view of the simultaneous occurrence of paresis and meningitis symptoms. He also discusses the possibility of simultaneous infection with both pol. myel. virus and men. enc. myel. virus.

In the German literature opinions are widely divergent. In 1936 Silbermann and Zappert discussed the diff. diagnosis thoroughly, without arriving at any definite conclusion — »meningitis serosa aseptica is a clinical form of expression for different noxae affecting the nervous system». In an earlier paper, however, Zappert had considered spontaneous enc. myel. to be an atypical pol. myel. In 1936 Assman and Vougts found nothing in cases of men. serosa appearing epidemically to argue in favour of pol. myel. from the epidemiological point of view, but speak of a disease *sui generis*. In 1937 Siegl described an epidemic at a day nursery in Vienna where, almost simultaneously, 7 children fell ill, 3 with typical pol. myel. and 4 with meningitis without paresis. He is of the opinion that the independent cases of serous meningitis occurring epidemically possibly have an independent etiology, while epidemics of pol. myel. appearing simultaneously argue in favour of the diagnosis aparetic pol. myel. The occurrence of

aparalytic aseptic meningitis cases caused by the poliomyelitis virus may be due to the character of the epidemic. In this connection he quotes Wieland of Basle, who considers that these meningitis forms are most usual in association with severe epidemics of poliomyelitis. The author also mentions that in 1932, during a pol. myel. epidemic, Uffenheim observed a »meningo-radicular form» resembling the aseptic pol. myel. not only as a prodromal stage to the paresis stage, but also as an independent disease. During an epidemic of meningitis serosa in 1936 Stender found no connection with pol. myel. He opposes, as for the rest do many other authors, the designation »aseptic», as its appearance in epidemics speaks against it. Molnár (1935) considered that only the course can determine the differential diagnosis. Kuhlmann (1941) considered the difficulty to be that the aseptic meningitis is not a disease *sui generis* but may have many causes.

Like many other American authors, Viets and Watts (1934) leave the question of the etiology open, but consider that the spontaneous men. enc. myel. are not abortive pol. myel.

From Denmark Lassen (1939) described a number of cases of primary serous meningitis and considers that they have the same etiology as pol. myel. Finally Gesell (1937) speaks of abortive, or rather meningeal, pol. myelitis cases and considers that 50 % of all pol. myel. run as meningeal forms.

This short survey of the research work of recent years by no means claims to be complete but only endeavours to give an idea of how opinions differ, and of how much still remains to be investigated.

A number of authors (among them Eckstein) are inclined, as has been pointed out previously, to see a certain connection between encephalitis lethargica and the aseptic men. enc. myel., or even to regard them as identical, but in our cases at least the symptom picture and the course are so different that it is difficult to conceive of any identity. Nor is there any reason why, in genuine encephalitis, the pathological process might not on some occasion also affect the grey substance of the midbrain. The diff. diagnosis from tbc-meningitis may then give rise to greater difficulty, and in the doubtful cases the course will be decisive.

It is improbable that men. enc. myel. should have any causal connection with the post-vaccinal encephalitis, *inter alia*, because

in so few cases has the simultaneous occurrence of men. enc. myel. and post-vaccinal nerve complications been observed. In the paper by Silbermann and Zappert referred to above, it is mentioned, however, that within a limited area 4 children fell ill at the same time, one with meningo-encephalitis symptoms (the father had had herpes zoster immediately before), one with serous aseptic meningitis and two with post-vaccinal disease in the central nervous system, one of them in the typical post-vaccinal encephalitis. Möller has also observed in Ångermanland the occurrence of post-infectious and genuine encephalitis concomitantly with post-vaccinal nerve complications, but he ascribes this to special geographical and epidemiological conditions. Grönlund of Hälsingfors writes in this connection »on the other hand in their mode of appearance and with regard to their clinical and pathological-anatomical conditions, the post-vaccinal and post- or para-infectious encephalites present such great similarities among themselves, that one begins to incline more and more to the opinion that all these encephalites have a common etiology, a neurological agent which is at present unknown. In the case of enc.-myelitic complications in infection diseases, the specific infection substance is said to play the same activating rôle as the vaccine virus is considered to do in post-vaccinal encephalitis». Many other authors are following the same line of thought.

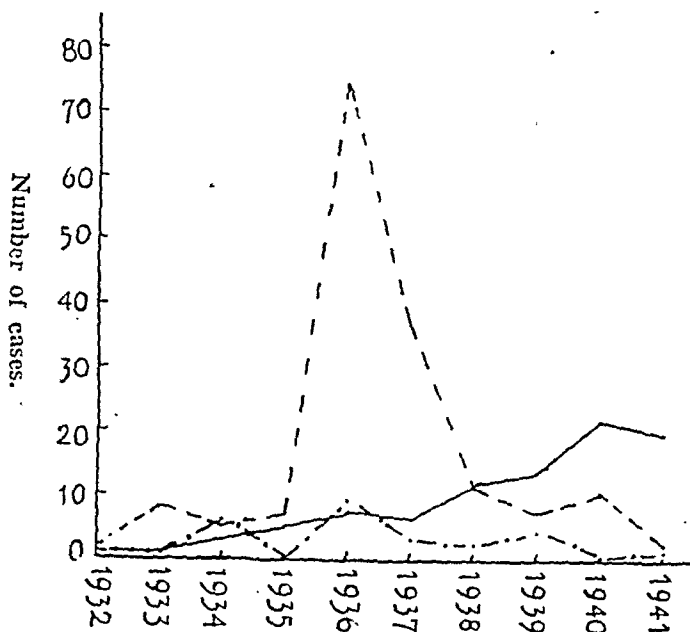
The above-mentioned epidemic encephalites with known etiologies, such as St. Louis enc., Japanese B-encephalitis, Australian X-encephalitis, and the acute lymphocytic choriomeningitis have — apart from the very serious prognosis — a graver morbid picture, and above all it has been possible to isolate the virus in all these cases, and the disease has also been successfully transmitted to experimental animals.

With regard to multiple sclerosis and especially acute multiple sclerosis, the diff. diagnosis is touched upon by a number of authors. The acute, which the majority of authors have obviously never seen themselves, but concerning which reference is nearly always made to other authors, only differs from men. enc. myel. in its course. The completely divergent clinical courses of men. enc. myel. and the ordinary multiple sclerosis make the diff. diagnosis less difficult. Finally, apart from the typical neurological changes, acute polyneuritis has a different fluid picture, but the diff. diagnosis

may present difficulties, especially in the men. enc. myel. cases which have polyneuritis symptoms.

A number of further diff. diagnostic difficulties, e. g. from tumor cerebri, lues, haematomyelia, etc., could of course be discussed, but the ones mentioned above are those which present the greatest difficulties.

During the 10-year period 1932—1941, 95 patients belonging to the group men. enc. myel. were treated at the County Hospital at Västervik. Of them 8 are not included in this discussion owing to incompleteness of case records and laboratory examinations.

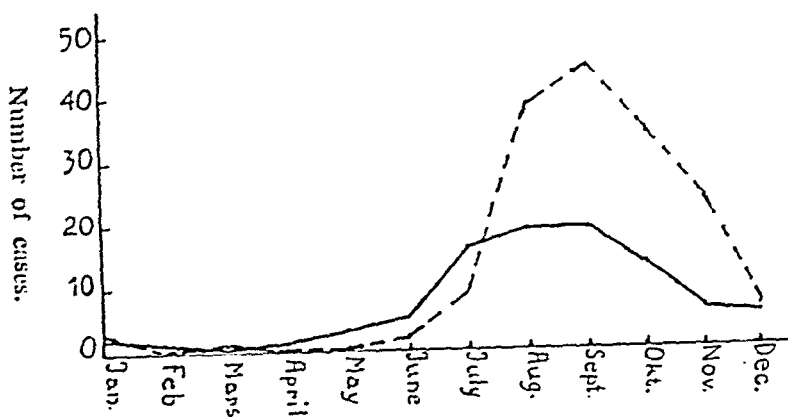


Curve no. 1. — Men. enc. myel. ---- Pol. myel. —.— Asept. meningitis.

There thus remain 87 cases, in addition to one case nursed at the Västervik Infectious Diseases Hospital in 1941, a total of 88 cases. During the same 10-year period, 163 cases were nursed at the Infectious Diseases Hospital under the diagnosis pol. myel. The reception area for the hospital is the northern County Council area of Kalmar Province, which had a population of c. 92,150 in 1940. As there is no other hospital within the district, all the cases which received hospital treatment will have been admitted either to this hospital or to the Infectious Diseases Hospital, which has the same reception area.

Curve no. 1 shows the distribution each year of men. enc. myel. cases admitted to the hospital and of pol. myel. cases, and of the

cases admitted to the Infectious Diseases Hospital under the diagnosis meningitis aseptica, encephalitis acuta, etc. The curve shows the increase in the last few years of our men. enc. myel. cases, 21 and 19 cases respectively during the last 2 years, while during the first 4 years of the 10-year period the number of cases was less than 5 per year. As is seen, this increase by no means goes hand in hand with an increase in the number of pol. myel. cases, rather the increase in men. enc. myel. cases shows a tendency to be accompanied by a decrease in pol. myel. cases. Of the cases admitted to the Infectious Diseases Hospital under the diagnosis

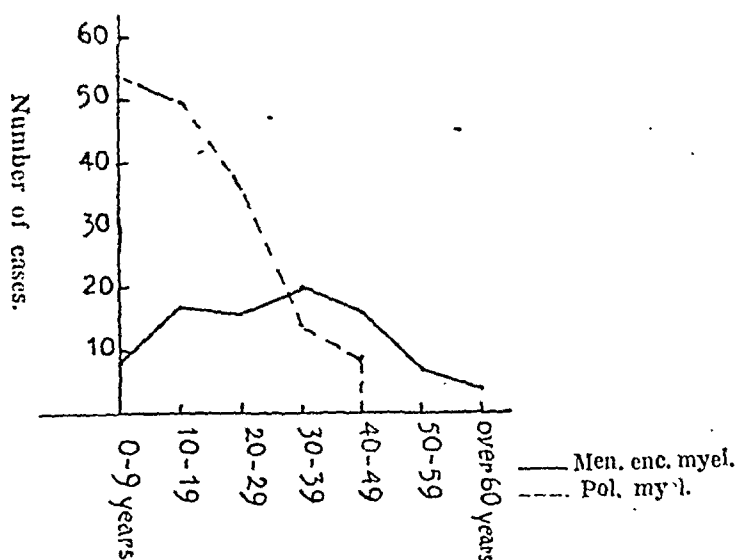


Curve no. 2. — Men. enc. myel. ---- Pol. myel.

men. enc. myel., the majority are not included in the discussion below, because the case records and the laboratory examinations made do not permit of a close study of each case. However, with the support of the case records the impression is obtained that the majority of the cases treated during the pol. myelitis epidemics in 1936 and 1937 were to be referred to the group abortive pol. myelites. During recent years, however, occasional cases of undoubtedly the same genesis as ours have been nursed at the Infectious Diseases Hospital, and we have had an opportunity of dealing more closely with one of them, so that it has been included in the discussion below.

The time of year for the onset of the first symptoms appears from Curve no. 2, where the seasonal distribution of the pol. myelites is also shown. As is seen, the curves run parallel, possibly with a tendency to onset earlier in the year for men. enc. myel.

pol. myel. cases is to be seen. Of the 20 pol. myel. cases at Virserum 19 fell within the year 1936. As an example may be taken the year 1940, with 21 cases of men. enc. myel., of which 3 were from Väster-vik, at intervals of more than one month between the cases, 3 from Gamleby parish, all from different parts of this large parish and at different times, 2 from Lofta with a month's interval between them. The rest were scattered cases from various parishes from the whole of the area served. In practically every caserecord it is noted that no case of pol. myel. had appeared in the neighbourhood. Only in one case had pol. myel. been established $1\frac{1}{2}$ km from the patient.



Curve no. 3.

The 88 men. enc. myel. cases are distributed over 55 men and 33 women, thus a preponderance for men of c. 62 %. Of the pol. myelites at the same time 102 were men and 61 women, i. e. here also c. 62 % men.

The age distribution of the patients appears from curve no. 3. As can be seen, there is no age of predilection for men. enc. myelitis. Between 10 and 50 years the cases are fairly evenly distributed — a clear difference as against pol. myelitis cases, where the number falls rapidly already at the age of 30.

The *anamnesic particulars* show a number of common features. The time varied considerably between the onset of the first sym-

ptoms and the admission of the patient to the hospital, between 3 and 21 days. It is of interest that in no less than 37 cases out of 88, i. e. nearly 41 %, the course had two phases, with a first acute sickening, in general 2—3 weeks before admission, after which the patient recovered but again fell ill, this time only 1—5 days before admission. During the intervening period, however, many patients stated that they had had headaches, fatigue and other more diffuse symptoms, but in general not worse than that they could remain at work. At the first onset the patient had most frequently had slight symptoms of meningitis, such as headache, nausea and often vomiting. It is worthy of note that, when they fell ill, 6 patients had pronounced symptoms of infection in the gastro-intestinal canal, and a further 3 had pains in the stomach but without diarrhoea. Six patients had symptoms of acute infections in the upper air passages. The other 22 began with no signs of other infection except slight meningitis symptoms. After a week at most the patient improved and in general began to work, only to fall ill again after a further 1—2 weeks, this time extremely acutely with pronounced meningitis symptoms and often other neurological symptoms, the latter never having been felt when the patient first fell ill. No difference could be observed between these 2-phase cases and the others with regard to the frequency of pos. neurological findings, course or prognosis.

In the majority of other cases the illness had an acute onset with high fever and frequently with shivering fits. Only 5 cases had never had a provable temperature, and 16 cases had been subfebrile with temperatures of 38° or under. 70 of the 88 cases had meningitis symptoms, above all in the form of headache, 50 cases nausea and vomiting. These figures are probably too low, as in many case-records particulars are extremely scanty as regards the anamnesis. 8 patients complained of stiffness in the neck. Aches in the body, usually in the back, were met with in 23 cases, vertigo in 17 cases, appreciable apathy in 13 cases, paraesthesia and subjective disturbances in sensibility in 6 cases. Paresis is found in the anamnesis in 10 cases, of which 3 had double vision, ataxia troubles in 4 cases, and one case each of motorial unrest and rigidity. The 51 patients without a 2-phase course generally had a shorter anamnesis. No tendency towards a 2-phase course could be discerned during the treatment here. Even though a

Table

No.	Sex	Age	Period nursed	Complications	Fever	S. R. max. mm/1 hr.	White blood corpuscles max. (1000)	Meningitis symptoms	Appreciable apathy	Pareses				Sensory disturbances	Spas- ticity	Extrapyramidal symptoms	Convulsions	Days after admission On admission	Nonne Pressure	
										Cranial nerves	Upper extremities	Trunk	Bladder							
1	♂	8 35			++	—	14.7	++	+									+	300	+
2	♂	32 16			+	30	9.0	+										++	150	(+)
3	♂	45 42			+	22	11.8	(+)			+			+				+	210	trace
4	♂	18 16			++	6	11.6	+									+	2	175	0
5	♂	26 69			++	33	8.4	++	+	Eyes	+			+				+	80	(+)
6	♂	28 23			+	39	9.4	(+)	+			+						+	140	0
7	♂	13 50			(+)	7	7.4	+		VII				+				19	220	++
8	♂	59 10			0	35	5.6	+	+								+		40	0
9	♂	28 8			(+)	55	8.4	+							+				100	0
10	♂	28 14			+	9	14.4	+	+					+					220	0
11	♂	48 28			+	30	9.8	++	+	XII							+		150	0
12	♂	31 25			+	24	7.8	0	+	VII									180	0
13	♂	66 20			+	32	6.6	0		VII	+			+					90	(+)
14	♂	59 46			+	30	7.6	+	+	VII						+	+		180	+
15	♀	12 31			(+)	6	9.4	0		VII									150	trace
16	♀	16 10			+	22	5.8	+	+	VII									230	0
17	♀	19 17			0	1	6.3	0	+	VII	+								120	0
18	♀	3 64			(+)	—	11.2	0		XII	+			+	+				—	0
19	♀	65 18			0	6	11.6	0	+	VII									295	+
20	♀	20 17			+	47	—	+						+				5	140	++
21	♀	40 15			+	38	8.5	+		VII									210	0
22	♂	21 36			0	—	8.5	0		XII	+	+							80	0
23	♂	24 46			++	55	9.0	+	+	VII							+	+	330	0
24	♀	48 33			++	24	—	+						+				7	140	trace
25	♂	43 36			+	—	—	+										10		+
26	♂	33 47			++	—	—	+	+								+		300	0

Note: Fever 40° and upwards marked ++, 38° — 40° : +, subfebrile: (+). Total protein

I.

Fluid maximal changes						Fluid minimum changes										Post examination							
Pandy	Total protein	Cells	Poly %	Mono %	Sugar mg %	Blood sugar mg %	Days after admission	Pressure	Nonne	Pandy	Total protein	Cells	Poly %	Mono %	Sugar mg %	Blood sugar mg %	Meningitis symptoms receded after days	Free of temp. after days	Free of symptoms	On discharge	Days after discharge	Remaining symptoms	
																							Remaining symptoms
++	1/20	10000	90	10	135		6	150	trace	trace	—	17	0	100			14	21	+				
+		262	20	80			9	150	(+)	+	1/40	26	0	100			9	5	+		120	+	
trace		22	0	100	85	80	30		(+)	+	1/20	11	0	100	85	80	10	30	+		35	+	
trace		71	16	84			12	200	(+)	+	1/10	36	10	90			7	7	+		44	+	
+	1/10	148	40	60	105	115	16	150	(+)	+	1/50	16	0	100	85	90	23	8	+				
+		98	32	68	80	70	18	130	0	+	—	7	0	100			10	14	+		30	+	
+++	1/40	560	12	88	90	55	0	100	trace	+	—	75	0	100	—	—	7	4					
trace	—	9	0	100	—												—	—	+		60	(+)	
trace	—	70	0	100	—												3	3	+				
0	—	3	0	100	—												3	5	+		1 y 60 d.	(+)	
(+)	—	10	20	80	—		8	120	(+)	+	—	3	0	100	—		12	2	+				
trace	—	50	2	98	—												4	5	+		1 y 30 d.	+	
0	—	76	29	71	—												4	4	+		6 months	(+)	
++	—	31	0	100	—																		
+	—	125	0	100	—												14	8	+		30 d.	+	
+	—	52	15	85	—													3	+		30 d.	(+)	
0	—	1	0	100	—													3	+				
trace	—	93	60	40	—												21	+					
++	1/20	208	0	100	—		10	220	0	(+)	—	29	0	100	—	—				+	30 d.	+	
++	—	59	0	100	—		0	130	+	++	—	27	0	100	—	—			3	3	+	30 d.	+
0	—	162	70	30	—		6	150	trace	+	—	80	?	?	—	—			2	4	+	14 d.	+
(+)	—	18	0	100	—						—									+			
0	—	26	10	90	—		5	100	0	0	—	3	0	100	—	—			7	14	+	11 months	+
+		125	?	?			16		trace	+		10	?	?					—	10	+	3 months	+
++		60	0	100			0	200	0	0		9	0	100					4	7	+	4 months	+
trace		40	?	?			10		0	trace		4	?	?					—	30	+		+

according to Bisgaard. Sugar determinations according to Krezelius-Seiffert.

Table

No.	Sex	Age	Days nursed	Complications	Fever	S. R. max. mm/hr	White blood corpuscles, max. (1000)	Meningitis symptoms	Appreciable apathy	Days after admission On admission	Fluid maximal changes				
											Pressure	Nonne	Pandy	Total protein	Cells
27	♀	49	22	Thrombosis	+	91	13.0	++	+	+	240/160	++	++	1/150	6500
28	♀	48	22		(+)	14	7.8	+	+	+	160	+	++	1/20	80
29	♀	34	22		++	70	17.6	++	+	+	250/110	++	++	1/30	7300
30	♀	34	76		++	36	—	+	+	+	220	trace	+	1/10	203
31	♀	54	23	Cholecystopathia	0	5	11.0	0	0	+	200	++	++	—	226
32	♀	55	53		0	13	4.2	0	0	18	170	+	++	1/30	186
33	♀	52	14		+	33	11.8	+	+	+	150	trace	+	—	62
34	♀	22	28		++	21	16.8	+	0	+	130	trace	trace	—	124
35	♀	32	13	Myocardiac injury	+	21	18.4	(+)	0	3	95	0	+	—	176
36	♀	13	15		++	38	15.2	+	0	+	260	trace	+	1/10	26
37	♀	11	43		+	6	7.4	++	+	+	95	+	++	—	600
38	♀	10	10		+	10	7.4	+	0	+	200	trace	+	—	51
39	♀	28	41	Hypertonia	++	—	—	+	0	5	140	+	++	1/20	140
40	♀	61	10		(+)	3	8.0	+	+	+	80	0	(+)	—	10
41	♀	30	17		+	15	5.2	0	0	8	180	++	++	—	153
42	♀	36	16		++	22	6.2	+	0	+	150	0	trace	—	44
43	♀	48	32		(+)	18	11.8	(+)	+	+	320	trace	+	—	43
44	♀	9	12		0	7	7.4	+	+	+	100	0	0	—	10
45	♀	49	18		+	24	10.1	+	0	+	210	trace	+	—	108
46	♀	52	10		0	34	4.8	0	0	+	190	trace	+	—	16
47	♀	8	9		+	12	10.3	(+)	0	+	110	0	trace	—	23
48	♀	9	8		+	—	7.2	+	++	+	225	+	++	—	460
49	♀	13	18	Abscess on the leg	+	—	—	—	+	+	130	++	++	—	299
50	♀	61	24		++	—	—	+	++	+	180	trace	trace	—	7
51	♀	29	11		++	2	9.2	0	0	+	125	++	++	—	18
52	♀	17	14		++	13	15.4	(+)	0	+	190	trace	+	—	100
53	♀	33	17	Enterocolitis	+	15	—	0	0	+	150	0	0	—	36
54	♀	13	10		+	30	—	0	0	+	180	+	+	—	39
55	♀	41	9		+	38	4.1	0	0	+	230	++	++	—	147
56	♀	34	14		+	26	7.4	++	0	+	210	++	++	—	44
57	♀	27	18		+	17	17.5	+	0	+	170	++	++	—	48
58	♀	17	42		++	22	—	+	+	+	250	0	trace	—	427
59	♀	54	30		0	37	9.8	0	0	+	165	++	++	—	310
60	♀	45	53		+	20	—	—	—	10	175	(+)	+	—	34
61	♀	35	30		+	—	—	—	—	14	—	+	+	—	64
62	♀	47	24		++	20	—	++	+	+	260	+	+	—	27
63	♀	30	31	Endometritis	+	—	—	+	0	+	320	0	trace	—	116
64	♀	34	48		+	6	9.8	—	0	+	350	+	+	—	100
65	♀	10	40		++	21	5.0	0	0	14	—	(+)	+	—	18
66	♀	34	27		+	17	—	0	0	+	230	(+)	+	—	29
67	♀	32	22		+	10	8.6	+	+	+	70	+	++	—	69

II.

II.		Fluid minimum changes														Meningitis symptoms receded after days	Free of temp. after days	On dis- charge		Postexa- mination	
		Days after admission	Pressure	Nonne	Pandy	Total protein	Cells	Poly %	Mono %	Sugar mg %	Blood sugar mg %	Remaining symptom	Free of symptoms	Days after discharge	Remaining symptom			Free of symptoms	Days after discharge		
96	4	16	170	0	trace	—	29	4	96	—	110	7	7	5	+	+	+	+			
3	97	7	130	0	trace	—	42	17	83	—	110	7	4	5	+	+	+	+			
64	36	2	300	trace	+	—	148	12	88	—	110	3	4	4	+	+	+	60			
4	96	10	100	+	++	1/30	83	2	98	—	110	3	4	4	+	+	+	21			
25	75	41	100	trace	+	1/10	31	0	100	—	110	7	4	4	+	+	+	60			
2	98	8	120	0	trace	—	4	0	100	—	110	7	4	4	+	+	+	75			
26	74	14	140	trace	+	1/20	16	0	100	95	110	14	8	8	+	+	+	78			
21	79	10	100	trace	+	—	28	0	100	—	110	11	8	6	+	+	+	97			
5	95	10	100	trace	+	1/10	6	0	100	—	110	8	6	6	+	+	+	15			
50	50	9	90	trace	+	—	6	0	100	95	75	12	98	14	+	+	+	50			
4	96	39	75	trace	+	—	47	2	98	—	110	3	2	2	+	+	+	15			
24	76	8	170	trace	+	—	6	0	100	—	110	14	6	6	+	+	+	50			
10	90	28	100	trace	+	—	42	4	96	—	110	14	6	5	+	+	+	21			
20	80	0	180	+	++	—	96	2	98	—	110	12	7	7	+	+	+	+			
0	100	4	60	0	trace	—	30	27	73	—	110	12	8	8	+	+	+	90			
48	52	0	100	—	—	—	—	—	—	—	110	2	16	+	+	+	+	+			
0	100	4	175	+	++	—	100	7	93	—	110	15	7	+	+	+	+	+			
20	80	6	170	trace	+	—	16	0	100	—	110	15	2	+	+	+	+	+			
0	100	12	100	+	+	—	158	0	100	—	110	3	3	+	+	+	+	+			
2	98	10	160	0	0	—	1	0	100	—	110	3	6	+	+	+	+	+			
1	99	10	160	0	0	—	1	0	100	—	110	3	5	+	+	+	+	+			
0	100	10	160	0	0	—	1	0	100	—	110	3	6	+	+	+	+	+			
0	100	10	160	0	0	—	1	0	100	—	110	3	7	+	+	+	+	+			
39	61	10	160	0	0	—	1	0	100	—	110	3	7	+	+	+	+	+			
?	?	10	160	0	0	—	1	0	100	—	110	3	6	+	+	+	+	+			
0	100	7	180	+	+	—	43	0	100	—	110	6	5	+	+	+	+	30			
2	98	9	120	+	+	—	8	0	100	—	110	6	4	+	+	+	+	14			
25	75	10	110	0	0	—	22	0	100	—	110	6	6	+	+	+	+	14			
0	100	30	+	+	+	—	31	0	100	—	110	6	6	+	+	+	+	14			
+	+	17	+	+	+	—	44	+	+	—	110	2	11	+	+	+	+	60			
0	100	20	0	0	0	—	12	0	100	—	110	7	7	+	+	+	+	+			
+	+	0	265	+	+	—	16	0	100	—	110	6	6	+	+	+	+	+			
?	?	15	+	++	++	—	11	0	100	—	110	9	9	+	+	+	+	+			
?	?	30	0	0	0	—	10	?	?	—	110	4	4	+	+	+	+	14			
?	?	22	0	0	0	—	13	?	?	—	110	2	2	+	+	+	+	45			
?	?	34	0	0	0	—	6	?	?	—	110	7	7	+	+	+	+	+			
?	?	16	0	0	(+)	—	3	?	?	—	110	5	5	+	+	+	+	+			
?	?	15	+	+	+	—	17	?	?	—	110	7	7	+	+	+	+	14			

Table

Table																
No.	Sex	Age	Days nursed	Complications	Fever	S.R. max mm/1 hr.	White blood corpuscles, max. (1000)	Meningitis symptoms	Appreciable apathy	Fluid maximal changes						
										Days after admission	On admission	Pressure	Nonne	Pandy	Total protein	Cells
68	+	60	18	Infection from teeth	+	16	—	+	0	+	200	0	+		120	
69	+	14	10		++	—	—	+	0	+	200	(+)	+		29	
70	+	31	8		+	18	—	+	+	+	200	0	0		6	
71	+	46	13		+	—	—	+	0	+	140	0	+		35	
72	+	46	12		(+)	—	—	+	0	0	110	0	trace		30	
73	+	45	29		++	5	—	0	0	0	150	0	trace		86	
74	+	28	19		+	—	—	+	+	+	150	+	+		150	
75	+	40	19		+	—	—	+	—	+	210	++	++		310	
76	+	15	10		+	—	—	+	+	+	240	trace	+		20	
77	+	21	35		+	15	—	+	+	0	210	+	++		25	
78	+	30	17	Angina	+	8	12.0	+	+	+	180	++	++		85	
79	+	34	31		+	4	—	++	+	+	120	0	0		6	
80	+	13	38		(+)	8	10.4	+	0	+	160	+	+		131	
81	+	29	23	Cholelithiasis	++	6	12.3	+	0	+	180	+	++		60	
82	+	28	18		+	47	6.2	+	0	+	200	0	trace		10	
83	+	9	30		+	30	9.0	0	0	+	110	0	trace		30	
84	+	31	18		+	15	—	+	0	0	180	trace	+		56	
85	+	30	12		+	6	—	0	0	+	210	trace	+		12	
86	+	7	32		+	10	—	0	0	+	130	0	trace		18	
87	+	10	13		++	—	—	+	+	+	160	0	trace		32	
88	+	35	28		+	22	11.2	+	+	+	220	+	++		42	

Note: Fever 40° and upwards marked ++, 38°—40°: +, subfebrile: (+) Total

number exhibited progress of the symptoms during the first part of the time, no free interval was established in any case. Only isolated cases among these cases had been preceded by or begun at the same time as any other infection disease, such as angina in 2 cases and occasional cases with diarrhoea, dental infection and mastitis.

The *status of the patients on their admission* was very much the same. Apart from weakness and fatigue, the subjective troubles, where there were any, were confined to headache, occasionally also to vomiting or nausea and aches in the body. From considerations of space, all the 88 cases are arranged in two tables; in table 1 are grouped together all with pos. neurological findings, and in table 2

II. (Continued)

II. (Continued)																
	Fluid minimum changes										Meningitis symptoms recurred after days	On discharge		Postexa- mination		
	Blood sugar mg %	Sugar mg %	Mono %	Poly %	Cells	Total protein	Pandy	Nonne	Pressure	Days after admission		Blood sugar mg %	Sugar mg %	Mono %	Poly %	Free of symptoms Days after discharge
+	0	100						0		6						
0	100				3	0	100									
0	100				1	0	100			10						
+					7	0	100			27						
0	100															
+																
+																
+																
+																
?																
+					3		+	trace	19	160					60	+
+					8		+	+	14						25	+
0	100														30	+
3	97				45		+	+	24						50	+
0	100				17	0	100	+	21						300	+
?															15	+
0	100				26	0	100	0	10	150					21	+
?					7	?	?	0	14	150						
?																
?																
?																
?																
0	100				6	?	?	0	21	130						
+					10		+	trace	18							

protein according to Bisgaard. Sugar determinations according to Krezelius-Seiffert.

the cases which — apart from meningitis symptoms — had a neg. nerve status. Unfortunately the notes in the caserecords and the laboratory examinations etc. are not always as complete as might be desired. This applies, above all to the fluid findings, where in several cases the cell type is not stated. In all the cases either W.R. or Meinicke was made, always with neg. result. Bacteria examinations in direct preparations were made in all the cases and showed neg. results, except in two cases, where occasional gram pos. and gram neg. diplococci were established at one examination — with a probability bordering on certainty this was due to pollution.

The periods in hospital varied considerably: 8—64 days, on an

average 26 days (29 for patients with pos. neurological findings and 22 for the others). Only somewhat over 1 % were entirely free of irregularity of temperature during their stay at the hospital, somewhat less than 1 % subfebrile, and 25 % had a temp. of 40° and upwards. The remainder, 73 %, had a temp. of between 38° and 39° during the first few days or at the height of the illness. No difference between group 1 (table 1) and group 2 (table 2). The most usual temperature course: high fever on admission, persisting for 1—3 days, then falling either lytically or remittently. Freedom from temp. on an average of 8 days. A number of cases, however, ran with an obstinately subfebrile temp. The sedimentation rate was moderately raised, in general about 30 mm/1 hr. In practically every case S.R. became normal already after 14 days. There was a moderate increase in the number of white blood corpuscles throughout, in general the values were normal already after the first week.

Among the neurological findings the meningitis symptoms predominate, above all stiffness of the neck. Patients with other neurological findings did not have more pronounced meningitis symptoms than those without. In 22 cases, i.e. 25 %, there was no stiffness of the neck, in 5 cases there are no notes on the point, and in 9 cases (10 %) the stiffness of the neck was strongly pronounced. Of these 3 (nos. 1, 27, 29) attract especial interest and differ in several respects from the others. 44 patients (10 %) were strikingly apathetic on admission or became so later; there are, not a few cases in which the illness progressed during the stay here which showed itself both in general and neurological symptoms and in the fluid finding. Which these cases were is shown in part by the tables, as the maximal fluid changes appeared some time after admission. It is a matter of 11 cases out of 88. As an example of this will be mentioned case no. 5, which is of interest also as an illustration of the diff. diagnostic difficulties in pol. myel.

It is the case of a 26-year-old married woman from Västervik, who was admitted in the autumn of 1941. From her anamnesis it appears that she had had typical attacks of migraine for many years, but had been healthy otherwise. Fell ill 12 days before admission with diarrhoea, pains in the abdomen and nausea. The stomach trouble ceased after 4 days, but the patient had then begun to have headaches, which had increased the last 3 days before admission. In addition, during the last few days

there had been nausea, vomiting and vertigo and repeated shivering fits. She had pain in the right shoulder and a feeling of weakness in the right arm and a numb sensation in both arms. When admitted, general condition affected, severe headache and nausea as soon as she lifted her head. Clear and lucid. Moderate stiffness of the neck, moderate paresis in the right arm, moderate but obvious ataxia in the right arm. Nerve status for the rest neg. Lumbar puncture: Pressure 80, Pandy +, Nonne weak +, 148 cells, of which 88 mono and 60 poly. Next day L.P.: 121 cells, of which 76 mono and 45 poly. 2 days after admission disimproved general condition, very apathetic, sleeps nearly the whole 24 hours but answers clearly and lucidly. Occasionally double vision, but no definite paresis of the eye muscles can be established objectively. The neck stiffness has increased. In the nerve status there is now moderate paresis of the right leg and right patellar reflex, and both the achilles reflexes are absent. L.P.: 87 cells, of which 79 mono and 8 poly. After 5 days better, not so apathetic, no headache or vertigo. Patellar and achilles reflexes absent bilaterally. Obvious ataxia in the right arm. Next day (6 days after admission) Pandy +, Nonne +, 25 cells, all mono. After 9 days: not so apathetic, slight stiffness of the neck persists. No paresis now provable, all reflexes normal. No ataxia. Temp. $40^{\circ}.4$ on admission, for 5 days 39° — 40° . After 8 days free of temperature. Later thrombosis in the left leg developed, which prolonged her stay at the hospital considerably. The last L.P. was made 16 days after admission: Pandy +, Nonne +, 16 cells, all mono.

Such a picture must naturally suggest pol. myel. It will ber discussed later why we did not consider that in this, as in similar cases, we ought to diagnose pol. myel.

The fluid changes when patients were admitted or at the height of the illness appear from the tables. In 28 cases (32 %) the pressure was above 200 mm; in 6 cases 300 and upwards. The albumen reactions were moderately increased, in general Pandy +, Nonne + or faintly +. In 8 cases neg. albumen reactions. Total determinations of albumen according to Bisgaard were made in a number of cases, and only no 27 shows values above $1/50$. The cell content per cm^3 maintained itself within moderate limits, except in cases 1, 27, 29. These 3 patients were admitted between Jan. and April 1941 from entirely different parts of the area served. The acutely onsetting, violent anamnestic symptoms, with high fever, violent headaches 2—4 days before admission are common to them. At the time of admission severely affected general condition, pronounced stiffness of the neck, pronounced apathy. Only no 1 exhibited for the rest pos. neurological symptoms, namely pos.

Babinski bilaterally. At L.P. high pressure, strongly pos. albumen reactions, and a large number of cells: No 1: 10,100 (90 % poly. and 10 % mono), no 27: 6,500 (96 % poly), no 29: 7,300 (64 % poly). It was in nos 1 and 29 that a number of diplococci were discovered in the fluid — probably due to pollution. For the rest the course is entirely parallel to that in the other cases, period in hospital between 22 and 35 days. All 3 were discharged completely free of symptoms. It is worthy of note that they fell ill at a time of year (Jan.—April) which is otherwise relatively free.

For the rest the largest number of cells remained within moderate limits, c. 80 per cm^3 , inconsiderably larger for cases with pos. neurological findings: 92 and 69 in cases without. The border values 1—600. In 76 % the mononuclear were in a clear majority, only 6 cases had predominatingly poly, namely — apart from the 3 cases 1, 27 and 29, mentioned above — nos 18, 21 and 68, and in one case poly=mono. With regard to cases nos 18 and 68, only one L.P. was made, and for case no 21 another L. P. was made after 6 days, but no note was made as to the type of cells. In 41 cases out of 88, mono were 90 % and upwards. In 14 cases there are no particulars of the type of the cells. It may be of interest to study how long after admission we still found pathological fluid findings. After 30 or more days after admission, 6 cases still had pathological findings, 9 cases 20 days after admission, and 24 cases 10 days after admission. In addition there is one case which is still being treated here after 2 months and still has pathological fluid changes. With regard to the 16 cases with pathological fluid findings persisting 20 days after admission, the number of cells varies between 6 and 61, on an average somewhat above 25, with above 88 % mono in all the cases (not including case no 7 which is still in hospital). There is no difference as regards the fluid changes established by us in cases with or without neurological changes. Further, it should be pointed out that in only 9 cases was the number of cells below 5 per cm^3 , at the last L.P. made, so that the figures adduced by no means elucidate the question of how long pathological changes in the fluid had persisted, but only show the changes at the last L.P. performed by us.

As regards the sugar content in the fluid, opinions are extremely divided as to how far it is justifiable to draw any conclusions from the values obtained, since a number of factors which have nothing

to do with the illness affect the sugar content. It appears from the tables that in the cases where the sugar content was determined, we found increased values, which are met with chiefly in the cases where blood determinations were made in direct association with L.P. The determinations were made according to the same method — the Krezelius-Seiffert. The mastic test was made in the majority of cases with pos. albumen reactions. In the cases where the reaction was not normal or was neg., there is a tendency to a displacement to the right, but this is by no means constant, so we have had no guidance from this reaction.

In tables 4 and 5 all the cases are collocated, and the *neurological* findings in the individual cases will be discussed below. It appears from table 4 that 26 of the 88 cases, i.e. 29.5 %, had positive neurological findings.

Extrapyramidal symptoms were present in 6 cases (8, 11, 14, 23, 25, 26). When discharged 3 of these had symptoms persisting in the form of a mask-like face, stiff gait, monotonous voice, and in case no 8 tremors also. Of these no 23 was entirely free of symptoms after 9 months, and case no 8 was fully capable of work after 2 months, and only a slight tremor persisted. No 26 did not return. Two of the cases, 11 and 14, were completely free of symptoms when discharged, and no 4 was still free of symptoms a month later. No 25 was discharged free of symptoms but had obvious tremors after 14 days. He received atropine, after which he improved, 3 ½ months after his discharge inconsiderable tremors persisted.

Thus, as far as we have had an opportunity of following them, of the 6 cases with extrapyramidal symptoms, 3 became entirely free of symptoms, and in 2 cases only slight tremors persisted at the last examination. One of the patients was discharged with slight persisting disturbances, and never returned. These cases differ in no respect from the others, as regards either the anamnesis, or the clinical findings for the rest, or the laboratory findings. To classify these cases as encephalitis lethargica solely with the support of the moderate and rapidly passing extrapyramidal disturbances appearing in all the cases in direct association with the acute onset, appears far-fetched, so much the more as the clinical picture for the rest does not tally with the usual description of encephalitis lethargica. Further, it should be noticed that extrapyramidal symptoms have also been described in cases belonging to the Japanese B-encephalitis group, which is clearly delimited from

lethargica. In all our cases the observation period is naturally too short to exclude sequelae of one kind or another. The possibility that encephalitis lethargica has changed its clinical picture has been discussed, and if it is considered that such is the case, it cannot be determined whether it is a matter of lethargica in our cases or not.

The cases with paresis are of great interest, in view of the diff. diagnosis as against pol. myel. In 17 cases out of 88, i.e. somewhat over 19 %, pareses were established.

Of these 8 were cases with cranial nerve paresis only, 7 of them facialis and 1 hypoglossus. The latter also had clear extrapyramidal symptoms, so the pol. myel. diagnosis was out of the question. With regard to the facialis pareses, the same applies to no 14. No 7 had also sensory disturbances. The other 5 had no other neurological findings (nos 12, 15, 16, 19, 21). Of the facialis pareses 3 were of the peripheral type, 3 of the central type, and 1 not indicated.

Of the other 9 cases with pareses, in one (no 3) the paresis was localised in the right hand, combined with paraesthesia and reduced tactile sensation in the ulnar side of the whole lower arm and ataxia in the hand. Two cases had paresis in the whole leg, and of them no 10 combined with sens. disturbances, no 24 paresis only. Among the other 5 cases (nos 5, 13, 17, 18, 22) no 13 had a central VII-paresis and a XII-paresis and reduced gross strength in the whole of the left arm and leg, but not abdominal paresis. In addition to paresis in the right arm and leg (no abdominal paresis), no 18 had VII- and XII-paresis and also spasticity in the right leg with pos. Babinski. No 17 paresis in the left arm and facialis. No 22 VII- and XII-paresis and bilateral shoulder paresis and slight left-sided abdominal paresis.

Thus, to sum up, there are altogether 10 cases with paresis only without sens. disturbances or other neurological findings, which might contribute to the diff. diagnosis as against pol. myel. Of these nos 17 and 22 ran an afebrile course, which, however, argues against pol. myel. In a number of these cases pol. myelitis etiology cannot be excluded with absolute certainty. It may be pointed out already at this point that in all these cases — apart from the facialis pareses — the paresis affected one or more extremities and not any special group of muscles. In no case was it a question of complete paralysis, but only of a reduction of the gross strength. Only in 1 case (no 5) were the reflexes lost. It was not possible to establish atrophy of the paretic extremity or extremities.

With regard to the other cases where no paresis was established, in 3 cases (nos 1, 4, 9) the neurological findings were confined to pos. Babinski, which, even if it does not exclude pol.myel., does not argue in favour of it. In one case (no 2) rapidly transient ataxia and paraesthesia in the hands, and in one (no 20) obviously livelier patellar reflexes on one side, but with neg. Babinski.

The *course* for the rest was as follows: The stiffness of the neck persisted on an average 8 days (in a number of cases no notes on this point). Entirely free of symptoms when discharged 13 out of 26, i.e. 50 %, of group I (with pos.neurological findings). Five of these were post-examined, on an average after a month, and were then still subjectively and objectively free of symptoms. Persisting pareses when discharged in 7 cases, in 2 of which (nos 3 and 12) the pareses had completely receded after 35 and 30 days respectively (no 12 still free of symptoms after 1 year and 1 month). No 10 still tired in the previously paretic leg after 1 year and 2 months. No objective pareses. Tactile and pain sensation still reduced in the leg. After 6 months no 13 slightly tired in the left leg — nothing objectively. No 17 persisting slight facialis paresis when discharged and no controls. No 19 unchanged facialis paresis after a month. No 15 improved after a month, but slight paresis in facialis persists. Thus, of the cases with pareses, there are five who, during our observation period, had subjectively or objectively persisting symptoms. As regards other neurological disturbances, no 2 was free of symptoms after 4 months, no 7 still in hospital. The 6 cases with extrapyramidal disturbances have been described above.

Group 2 (table 5) with practically neg. nerve status as regards meningitis symptoms, comprises 62 cases. Of these 61 were discharged free of symptoms, while one complained of moderate headache. He did not return, so the trouble has probably disappeared. The table shows the control examinations after discharge. 24 patients returned after periods varying between 14 days and 10 months. Of them there were only 2 who then had any trouble, namely no 55, who complained of vertigo when he worked in a bowed position, which need not necessarily be ascribed to his meningitis, and no 35. The latter was discharged free of symptoms, but returned after a month and then complained of stiffness of the neck and sleeplessness. After a time increasing neurasthenic

trouble — forgetful, irritable, difficulty in collecting his thoughts, sleepless, etc. He was re-admitted 2 ½ months after discharge. Nerve status completely neg. L. P.: Pandy slightly +, Nonne slightly +, 3 cells, all mono. Already on the day after admission felt free of symptoms and was discharged after 2 days. One month later free of trouble, apart from a certain fatigue. Objectively 0. In this report no attention has been paid to the fact that on discharge many patients felt tired and weak, which symptoms, however, soon disappeared.

With regard to the *prognosis*, it may be pointed out by way of summary, that as far as we have had the opportunity of following the cases, 79 of the 88 patients, i.e, nearly 90 %, became entirely free of symptoms. One patient is still being nursed here. Of the remaining 8, as far as we can ascertain, none are incapable of work or have their capability for work reduced in any degree worth mentioning. We have had no deaths. As has already been pointed out, however, the observation period is too short for it to be possibly to draw any definite conclusions as to later results. In this connection Rydén's reports from the Psychiatric Clinic in Lund, where in many so-called neurosis cases, psychoneurosis cases etc., slight encephalitis conditions have been established, often with slight extrapyramidal disturbances, is of interest. The symptoms which led to admission to the Psychiatric Clinic often appeared insidiously, frequently after some known infection illness, in other cases without the patient's being able to trace the troubles back to any definite point of time. It still remains to be seen whether any similar troubles will arise among our cases.

As appears from what has been said above, the question of the *etiology* and *differential diagnosis* of these men. enc. myelites is of great interest. It appears probable that the majority of our cases are to be referred to the same etiological factors. The 3 cases mentioned above, nos 1, 27 and 29, which in certain respects differ from the others, might be exceptions, and also the cases with extrapyramidal symptoms, but it has already been pointed out that their agreement in the anamneses, neurological findings and course, with the majority of cases is so complete that we considered that we could place these cases with the others. As regards our cases, and also as regards those of other similar aggregations of men. enc. myel. described by other authors, the problem seems to

me to be whether we are dealing with a disease sui generis, or whether it is a question of pol.myelites.

For many reasons it is dangerous, and often impossible, to draw any definite conclusions from epidemiological factors. Firstly, the epidemiology of poliomyelitis has not been incontrovertibly elucidated, secondly, our figures are too few. Certain points of view, however, are deserving of attention with all reservation for the paucity of our material. No aggregation of cases from certain places or even adjacent places has occurred; on the contrary the cases are evenly distributed over the whole area served. In none of our cases had the persons concerned been in contact with any similar disease or with pol.myel. During the 10-year period, men. enc.myel. cases increased fairly constantly, independently of the increase or decrease of pol.myelitis cases. In the years 1936 and 1937 a severe pol.myelitis epidemic raged here, with 111 certain cases of pol.myelitis. At the same time there were 12 cases being nursed at the Infectious Diseases Hospital under the diagnoses: aseptic meningitis, acute encephalitis, etc. Of these, 2 were cases of typical parotitis encephalitis, and 2 cases with extrapyramidal disturbances. There remain 8 cases which might have been, and probably were, abortive pol.myel. At the same time there were nursed at this hospital 13 cases of men.enc.myel., of which one with extrapyramidal disturbances. The others agree in all respects with the picture of men.enc.myelitis described previously, but, apart from the meningitis symptoms, had no neurological disturbances. It is obvious that among them may be cases of abortive pol.myel., just as among the Infectious Diseases Hospital's cases of suspected abortive pol. myel. there may be concealed men. encephalitis of another genesis. In 1940—41 we had 40 cases of men.enc.myelitis, and at the same time 12 cases of pol.myelitis and the case of men.enc.myel. previously mentioned, which was included in our figures, were nursed at the Infectious Diseases Hospital. If our cases were abortive pol.myel., one would be justified in expecting a large number of definite pol.myel. with pareses during this period, unless it is to be assumed that the pol.myelitis epidemic had changed its character just during the last few years, and that cases now appear abortively without pareses. Even if this were the case, 11 of our 40 cases had such neurological disturbances that the diagnosis of pol.myelitis is excluded.

With regard to the ages of the patients, the differences as against the pol.myel.nursed at the same time is striking, as has been pointed out above. Up to the age of 50 the number of men.enc.myel. is evenly distributed.

The anamneses afford no definite criteria, pol.myel.may also have a 2-phase course. In the »status on admission», the hyperaesthesia and tenderness on pressure typical of pol.myel., and also the sweatings, are nearly always absent, on the other hand many of our cases were strikingly apathetic, in a number of cases almost lethargic, but never comatose. The meningitis symptoms remained a remarkably long time, on an average 8 days; and in 16 cases, as has been pointed out above, the fluid changes still remained 20 days after admission. (It must be noted that this figure is obviously too low, as it only refers to the last lumbar puncture made by us). It has proved to be a difficult matter to find in the literature particulars of how long the fluid changes persist in pol.myel., but it may probably be calculated that the fluid finding will be normal 2—4 weeks after the onset. If this figure is correct the changes remained a remarkably long time with some of our patients. There is an additional noteworthy fact. The fluid changes in pol.myelitis are maximal about at the same time as the pareses make their appearance, i.e. in the majority of cases at the time of admission for treatment at the respective nursing institutions, or during the first few days afterwards. Of our 88 cases 11 had a progressive course of the illness during the first period of treatment with increasing fluid changes, and of these only 1 case (no 24) in association with the appearance of a slight paresis (without reflex disturbances) in one leg. As has been stated above, in no 5 the fluid changes had receded when the pareses in the legs set in. In the majority of our cases, both with and without pareses, the pleocytosis was so moderate that at least it did not speak in favour of pol.myelitis.

As regards the type of cells, predominatingly nuclear are expected at the beginning of a pol.myelitis, i.e. at the point of time of the appearance of the maximal fluid changes. When it was possible to ascertain the number of cells, only 6 of out 74 cases had predominatingly polynuclear. For the rest mono. were clearly predominant. Thus, the fluid finding cannot be made the basis

for the diff. diagnosis, but our fluid findings are at least not typical of pol. myelitis.

The neurological changes have been exhaustively discussed above, and here it will only be briefly repeated that, apart from cases with isolated cranial nerve pareses, whole extremities were affected, and further that only in one case were the reflexes lost. Even in the cases with paresis in both arm and leg on the same side, there was no corresponding abdominal paresis. We were not able to establish in our cases the muscle hypotonia typical of pol. myel. Apart from a couple of facialis pareses, the prognosis was extremely good — all completely capable of work, and at control examinations no objective signs of pareses. We were never able to establish any atrophy. These facts appear to argue against pol. myelitis. Further, 3 of the doubtful cases with paresis had an afebrile course, which could hardly have been the case if the diagnosis had been pol. myel. (nos 17, 19, 22).

We consider that we have good reason to regard the majority of our cases as men. enc. myelitis sui generis of unknown etiology, and not as pol. myelites. Certain cases are doubtful and might have been pol. myel., but this does not apply to the majority. We have had no possibilities of deciding what etiological factors caused the disease. The homogeneous character of the cases makes it improbable that several etiological factors played their part, nor, except in a number of cases with diarrhoea and occasional cases with angina etc., had the patients had at the same time any other observable infection illness which might have caused men. enc. myelitis, or in any way prepared the way for a possible latent neurotropic virus. No accumulation of cases in association with or concomitant with small-pox vaccination was met with, and during the 10-year period one case of vaccination encephalitis occurred, i.e. in 1932. As no case ended fatally, we had no opportunity to study the pathological-anatomical changes.

Before the sulphonamide era, the treatment was purely symptomatic. During the last few years the patients have invariably been given sulphonamide or sulphathiazol. It is doubtful, however, whether this therapy has affected the course to any degree worth mentioning.

Summary.

During the 10-year period 1932—1941, 88 cases of men.enc. myel. were nursed at the Västervik Hospital and 163 cases of pol. myel. at the Västervik Infectious Diseases Hospital. After an account of the anamnesis, clinical findings and prognosis for men. enc. myel., the differential diagnosis, especially as against pol. myel., is discussed. The following facts emerge:

1. There occurs no aggregation of men.enc. myel. cases from one and the same place and at the same time.

2. Men. enc. myel. has shown a tendency to increase in the last few years, but the increase does not coincide with pol. myel. epidemics. Nor did men. enc. myel. increase more appreciably during the pol. myel. epidemic in 1936—1937.

3. If our cases were pol. myel., it would be justifiable to expect that several definite pol. myel. with pareses would appear at the same time, unless it is to be assumed that pol. myel. has changed its character and now appears as abortive aparalytic pol. myel. Even if this were so, several of our cases had such neurological findings that they exclude the diagnosis pol. myel.

4. No age predilection for men. enc. myel.

5. The hyperaesthesia, sweatings and tenderness on pressure typical of pol. myel. are absent.

6. The meningitis symptoms and fluid findings persisted for a strikingly long time.

7. The pleocytosis was moderate and the pareses did not appear simultaneously with the maximal fluid changes.

8. In the cases where there were pareses (19 %) — apart from the cranial nerves — whole extremities were affected and not isolated groups of muscles. No muscle atrophy was met with.

9. With reservation for the short observation period, the prognosis was extremely good. No deaths. Nearly 90 % entirely free of symptoms. None of the remainder incapable of work.

With this support, we consider that we have well-founded reason to regard the majority of our cases as men. enc. myel. sui generis of unknown etiologies.

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A study of cancer frequency in Stockholm.

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The question as to whether cancer diseases are actually on the increase is an old subject of debate in all civilized countries. The development of diagnostic methods in relation to cancer, as well as improved and extended facilities for medical attention have led to a more frequent diagnosis of cancer than formerly. The higher average length of life also entails an apparent increase in cancer frequency in respect of the total population.

One may follow cancer frequency in relation either to the morbidity or to the mortality.

The morbidity may be studied through the statistics of hospitals and cancer bureaus. But with neither it is possible to follow cancer frequency back for any considerable length of time into the past. The difficulty of arriving at the total cancer morbidity by means of circularizing the medical profession is shown by the enquête undertaken by Fibiger in Denmark in 1908. 98 % of the physicians throughout the country took part; and the cancer morbidity arrived at from the answers sent in was 4.3 per 10,000 inhabitants. That this is far below the true figure is best shown by the fact that the cancer mortality for the same year was 13.4 $\frac{0}{000}$ according to the official statistics.

In the year 1920 Nyström published an investigation of the Swedish Cancer Society into cancer diseases in Sweden carried out

during the period 1911—13. At least during the first year the physicians in Sweden took part in this enquete almost to a man; and the cancer mortality arrived was 5.9 ‰ while according to the official statistics the cancer mortality was 10.2 ‰. Nyström commented as follows: »The material obtained by this enquiry is of course not so complete as to justify its use as a basis for a reliable statistics of the morbidity in respect of the total frequency. For the years 1911 and 1912 it may be assumed to cover only rather more than half the number of actually occurring cancer cases; and for the year 1913 considerably less. On the other hand, however, the comparatively large material may well give us a good idea of the relative frequency of different cancer diseases.»

The mortality may be studied in the official statistics and in insurance or post-mortem statistics. Bergstrand and Reutervall (24 p. 15—17), who investigated 5200 post-mortems carried out in Stockholm during the period 1909—15, found that nearly 17 % of the cancers discovered in this connection had not previously been diagnosed. Four percent of the clinically diagnosed cancers in the material were not verifiable on section. Earlier German and Hungarian investigations, which also covered material from large hospitals, arrived at still higher figures. The development of diagnostic methods has of course diminished the number of undiagnosed and clinically misrepresented cancers; but as late as 1921 Lubarsch gives figures for a large German post-mortem material which are comparable with the above-quoted Swedish figures. Lubarsch considers that cancer-frequency can be studied only in connection with post-mortem material. In support of this view he adduces the fact that the figures yielded by a large German post-mortem material were 9.4 % of the females and 8.8 % of the males, while the corresponding figures according to the official mortality statistics were 6.4 % and 5.0 %. The difference may, however, be due to a different age-classification of the material.

One disadvantage of the post-mortem statistics is that they cover such a relatively limited material. Lubarsch states that only 4.1 % of those who died in Germany in the years 1920—21 were subjected to post-mortem examination. Wood has pointed out that the mortality statistics based on post-mortem investigations are seldom representative, for they are often taken from hospitals where special diseases predominate. Therefore, the total frequency of a disease

for different periods cannot be ascertained from post mortem statistics.

A number of authors (2, 12, 14, 17, 18, 27, 28) maintain that a supposed increase of cancer of the lung, which is shown by post mortem statistics, is merely an illustration of the unreliability of such statistics as a gauge of frequency of a disease. According to Lubarsch, German post mortem material from 1920 shows that only 50 % of the lung cancers that were found in the sections had been diagnosed before death. Thus the assumption that cancer of the lung is to a great extent clinically undiagnosed still holds good. The markedly increased interest in the diagnosis and therapy of this disease must result in its discovery more frequently than has hitherto been the case. The statistics for lung cancer for the last twenty years, during which period the alleged increase in frequency is supposed to have taken place, vary so widely that most writers, who have dealt with the question consider this fact alone to be sufficient indication that actually no rise in the frequency of cases of lung cancer has occurred.

In studying the cancer rate over a longer period of time one is generally compelled to have recourse to the official mortality statistics. Progress has been made in the treatment of cancer, so that especially patients with external cancers are completely healed and others cured for longer or shorter periods, and may thus die of other diseases, in which case cancer is not the cause of death. The diagnostic improvements probably play a more important role for the statistical figures than the therapeutic progress. The possibility of clinical diagnosis, especially of the relatively early stages of internal cancers, has undergone a rapid development. On the other hand, it may safely be affirmed that physicians many decades ago were able with about the same assurance as now to recognize the final stages of even the less easily diagnosed cancers. The older mortality figures are thus probably more comparable with the later ones than is the case with corresponding morbidity figures.

Comparison of the figures for cancer mortality from different countries and periods must be used with certain caution. The proportion of physicians, the organization of medical attention and the population statistics must all be taken into consideration. To illustrate the importance of the role played by such factors it may be mentioned that the official cancer mortality in Lithuania was 3.4⁰/₁₀₀.

while at the same time in adjacent parts of East Prussia it was 11.5 ‰. In Czecho Slovakia the official statistics for Carpatho Ukraine during the 1920's showed an increase of the cancer mortality by 170 % as against 40 % Moravia. This remarkable difference might be explained by the fact that after the World War the population statistics and the medical attention were more thoroughly revised and improved in the eastern parts of the country than in the western provinces.

There is reason to suppose that the rise of frequency of cancer with civilization is more apparent than real. That the figures for backward people are lower than those for more civilized is chiefly due to the internal, more difficultly diagnosed cancers. A number of investigations have shown that the external, easily diagnosed cancers are commoner among coloured peoples than among whites. Hoffman has shown that the cancer frequency among negroes in the U. S. A. comes progressively nearer that of the whites as the negroes receive increased possibilities of medical attention and hospital treatment, so that their morbidity and mortality statistics are rendered more reliable.

According to older statistics, cancer-mortality is throughout considerably higher for women than for men. This difference between the sexes, however, tends everywhere to diminish; and in Switzerland, where the mortality statistics are very accurate, it has disappeared completely. The reason why this difference was formerly so marked was probably that the cancers in men comprise in a higher degree, than is the case with women, the less easily diagnosed internal cancers, such as for instance cancer of the ventricle. The large group of cancers of the breast and of the uterus in women, on the other hand, may be regarded as relatively easily diagnosed.

The therapeutic progress in connection especially with the easily diagnosed cancers is the strongest argument for those who consider that mortality figures are of no use for the study of cancer-frequency (Peller). It should be emphasized, however, in this connection, that according to a number of statistical investigations (25, 30, 35) death from mammary cancers is on the increase, while death from cancer of the uterus is diminishing, despite the fact that the former is easier to diagnose and responds more readily to treatment. The difference in frequency is probably to be ascribed to diminished nativity, for the mothers of large families are said to

be more liable to cervix-uteri-cancers than are sterile women, while the latter are supposed to be more subject to mammary cancers. That the cancer-mortality in urban districts is generally higher than in the rural may be due to more reliable diagnosis in the former. It is, however, possible that a different age-grouping in urban and rural populations may play a part. In an investigation from Saxony Freudenberg has shown that an increase in the number of medical practitioners coincides with a higher cancer-mortality. Although in Swedish towns, in contradistinction to the country districts, a diagnosis by a medical practitioner has been required in all cases of death since 1859, the difference between cancer-mortality in the towns and that in the country is surprisingly small in Sweden. If as a basis of comparison we take 100 to represent the cancer-mortality in Swedish towns, the corresponding figure for the country districts is for the last thirty years between 92 and 94. The corresponding figure for the country districts in Canada is 60; but in a densely populated country like Holland this difference between rural and urban figures does not occur; in certain parts of the country the rural figures are even higher than those for the towns.

Figures of this kind, however, cannot be regarded as conclusive, as they do not take into account the differences in age-grouping. Better diagnosis could be expected to show considerably higher cancer-mortality in the towns. This may be counteracted by a higher percentage of old people in the country, due to a strongly marked influx of young and middle-aged people to the towns from the country districts.

According to older statistical investigations, as for example the above-mentioned enquiry published by Nyström, the well-to-do classes showed a higher cancer-mortality than the poorer classes. This, however, may be explained by the fact that the well-to-do had formerly much readier access to good medical treatment and accurate diagnosis. Recent investigators (16, 40) state that cancer-mortality — especially in the case of ventricular cancer — diminishes with increased social well-being. It has unfortunately not been possible for me to obtain a modern Swedish cancer material that would enable a grouping in social classes.

It is generally conceded, that workers with ready access to alcohol show abnormally high cancer mortality. This is especially remarkable as this group has a strikingly low average length of life.

In the study of the cancer mortality of various trade groups and social classes it is difficult to get comparable material from the point of view of age. Investigators who ignore this source of error can of course arrive at any conclusions whatsoever.

At the end of the nineteenth century people were impressed by the increase in cancer cases in official statistics, and it was generally believed, that an actual rise of cancer frequency was occurring. Articles in *Zeitschrift für Krebsforschung* at this time show, moreover, that great interest was taken in explaining the increase. It was, for instance, believed that cancer was commoner in certain dwellings than in others; and attempts were made to find a clue to the mystery in this alleged fact. The possibility of different ages of the inhabitants of the dwellings was not discussed.

As early as at the end of the 1880's, English authors asserted that cancer mortality was increased more rapidly among men than among women. They attributed this to more accurate diagnosis.

In the earlier discussion and in the papers referred to above there was a general tendency to overlook the different age grouping in the materials; only some of the older writers avoided this mistake.

In 1893 King and Newsholme published an important work in which they critically examined the increase in the statistics of cancer mortality. Their material comprised the official mortality statistics in Frankfurt-am-Main, which ever since 1860 have permitted of age analyses for various diseases. In addition they had access to a well differentiated — in point of age and cause of death — English life-insurance material. King and Newsholme arrived at the result that the increase in cancer-mortality was only apparent. They asserted that only the difficultly diagnosed cancers had increased, and that the increase was most marked in the highest age-groups. Weinberg and Gastbar, who ten years later investigated material from both Frankfurt-am-Main and Stuttgart, arrived at similar conclusions.

In more recent literature we still find authors in the 1930's who are of the opinion that cancer is actually on the increase. In general, however, the writers who have dealt with this question assert that a statistically satisfactory investigation of cancer-mortality give no support for the assumption that cancer is increasing.

Moreover, Peller, Theilhaber, G. Wolff, Wyss and others, basing their assertion on the figures for cancer-mortality from the last two

decades, consider themselves in a position to show that cancer is decreasing. These writers have studied mortality statistics from Switzerland, some big German cities, Vienna, Copenhagen and New York. As regards Switzerland, it may be mentioned that during the 1920's only 1.6 % of the deaths were not diagnosed by physicians; and in other respects also the mortality statistics are more accurate than those of most other countries. Great importance has been attached to the fact that in Switzerland also the mortality from difficultly diagnosed cancers has decreased during the last two decades.

In Germany the figures for cancer-mortality show a decrease during and just after the World War; but one cannot ascribe much significance to this, considering how civil care of the sick must have suffered under war conditions. Mortality statistics in Berlin show a consistent decrease of cancer since the first World War; but the interpretation of this phenomenon must be in so far equivocal as these statistics do not exclude the country-dwellers who die in Berlin. As regards the rest of the above-mentioned cities, it would seem probable that cancer-mortality is actually diminishing. It is, however, still too early to venture an opinion as to whether this decrease may also be regarded as applying to cancer-morbidity.

In the year 1859 it was made incumbent upon Swedish physicians to make out certificates of death for deceased persons who had been under their care during their last illness. Further, it was ordered that in the urban districts medical certificates should be filled in for all deceased persons and that these should be sent in to the municipal Board of Health (hälsovårdsnämnderna) after the clergy had transcribed from them the relevant data for the Death Register. In 1864 the municipal Officer of Health (stadsläkaren) in each town was charged with the task of drawing up a yearly table of causes of death on the basis of these certificates. From 1864—70 the Medical Council (Sundhetskollegium) published each year a survey of causes of death in the towns and cities of the kingdom on the basis of these tables. As early as 1861, however, the head of the Central Statistical Bureau, Dr F. T. Berg, had used the data given in the parish Death Registers to draw up annual surveys of the causes of death in the towns. These surveys were in 1863 discontinued for

all towns except the City of Stockholm, for which they were continued until 1867. From 1864—67 we thus have a double set of statistics of the causes of death in Stockholm; and a comparison between them shows that the reports of the municipal Officers of Health were less complete than those of the Central Statistical Bureau. It was not until 1870 that the death certificates sent in to the Senior Officer of Public Health (förste stadsläkaren) in Stockholm were satisfactory. In this year the Senior Officer of Public Health, Dr Grähs, issued for the first time as an independent publication a »Statistical Survey of the Causes of Death in Stockholm». The causes of death were here classified according to sex, age and communities. From 1871 onwards these statistical data were collected by a special municipal official; and after 1881 they were included in the annual report of the City of Stockholm Board of Health to the Medical Board. Stockholm has thus had more detailed and more differentiated mortality statistics than the rest of the kingdom.

In 1891 Professor Klas Lindroth drew up an exceedingly valuable synopsis of the causes of death and of mortality in Stockholm for the years 1871—1890. The work was published as an appendix to the annual report of the City of Stockholm Board of Health for the year 1891.

To follow the frequency of cancer-mortality in Stockholm I have arranged the official cancer-mortality figures for this city during the five-year period 1934—1938 in the same way as Lindroth.

By choosing a five-year period for comparison with the earlier twenty-year period one obtains absolute figures of comparable magnitude. Since the turn of the century Stockholm's annual cancer-mortality over five-year periods has on an average increased from 10.2 to 15.3 per 10,000 inhabitants. The corresponding figure for ages over 50, within which during the last decades at least 80 % of the cancer-mortality falls, lies between 52 and 56 per 10,000 inhabitants. The periods 1905—10 and 1934—38 have the same figure, namely 56⁰/₁₀₀₀. The averages for the annual cancer-mortality during five-year periods from 1871—90 lie between 9.9 and 10.6 per 10,000 inhabitants. For the first and last five-year periods the figure is the same, namely 10.2 per 10,000 inhabitants.

The annual cancer-mortality for the whole population of Stockholm, has increased from 10.2 ‰ during the period 1871—90 15.3 ‰ during the period 1934—38. During the former period cancer comprised 4 % of the total mortality, and during the latter period 15 %.

When drawing conclusions from these figures one must consider the age-grouping of the population as well as the mortality for children and young people during the different periods. Mortality in the age of 1—10 years was ten times higher during the earlier period than during the later one. As appears from table 5, mortality up to the age of 60 years was considerably higher from 1871 to 1890 than from 1934 to 1938.

During the earlier period the ages over 60 years constituted 7 % of the population, and during the later period over 11 %. From 1871 to 1938 the population of Stockholm was more than doubled ($\times 2.4$). During the same period the population in the ages over 60 years has been multiplied by 32 and in the ages over 80 by 75.

In order to get a clear picture of the cancer-frequency it is thus necessary to study the cancer-mortality in different age-groups. In this connection I have followed Lindroth's classification according to sex and in age-groups of twenty years. Lindroth's work also includes tables over cancer-mortality in the digestive and female genital organs.

Table 1.

Cancer-mortality in Stockholm, absolute figures.

Age-group	Men		Women	
	1871—90	1934—38	1871—90	1934—38
0—20 years	6	—	6	2
20—40 "	84	34	192	110
40—60 "	566	621	1076	768
60—80 "	432	1041	1090	1218
over 80 "	17	123	114	209
all ages	1095	1819	2478	2297

Table 2.

Annual cancer-mortality in Stockholm per 10,000 inhabitants.

Age-group	Men		Women	
	1871—90	1934—38	1871—90	1934—38
20—40 years	1.3	0.7	2.6	1.8
40—60 "	19.2	18.4	24.3	18.7
60—80 "	70.5	99.6	64.6	69.9
over 80 "	87.6	195.3	93.0	130.2
" 60 "	71.1	103.4	66.5	75.0
all ages	7.0	15.2	12.8	15.4

Table 3.

Annual cancer-mortality in digestive organs per 10,000 inhabs in Stockholm.

Age-group	Men		Women	
	1871—90	1934—38	1871—90	1934—38
20—40 years	0.8		1.1	
40—60 "	17.3	11.6	9.7	5.0
60—80 "	62.2	61.8	35.7	35.8
over 80 "	57.1	123.8	50.3	78.9

Table 4.

Annual cancer-mortality in female genital organs per 10,000 women in Stockholm.

Age-group	1871—90	1934—38
20—40 years	0.9	1.2
40—60 "	10.1	11.0
60—80 "	15.4	20.5
over 80 "	15.1	20.0

Table 5.

Annual mortality in Stockholm per 10,000 inhabitants.

Age-group	Men		Women	
	1871—90	1934—38	1871—90	1934—38
20—40 years	135	32	83	27
40—60 "	327	121	152	76
60—80 "	718	642	467	513
over 80 "	2242	1015	1869	914

Lindroth is struck by the fact that in his material the cancer-mortality among males is higher than among women in the ages 60—80 years. For the total population, the average figure for the cancer-mortality among men is 7.0 as against 12.8⁰/₀₀₀ for women during the period 1871—90. Moreover, as far as is known there are no statistics from the same period which in any age-group show excess-mortality from cancer among men. As has already been mentioned, we have reason to assume that the higher cancer-mortality among women has been only apparent. It is valuable to find support for this assumption in such old statistics as Lindroth's. During the period 1934—38 the cancer-mortality figures for the total population in Stockholm are practically the same for both sexes — 15.2⁰/₀₀₀ for men and 15.4⁰/₀₀₀ for women. Only the ages from 20 to 40 years show a distinct excess for the women. In the age 40—60 years cancer-mortality is practically the same for both sexes; and over 60 years the men show nearly 30 % higher cancer-mortality.

Table 2 shows that cancer-mortality has diminished in the ages under 60 years for both sexes. In the ages 20—40 years it has diminished by nearly 50 % for the men and at least 30 % for the women. This decrease may conceivably be explained by the fact that it was formerly more difficult than it is now to distinguish sarcomata and other tumours from cancer. However this cannot, constitute any source of error worth mentioning, for also during the last period (1934—38) we find only a few such tumours per year and age-group in the mortality-statistics.

The decrease in cancer-mortality in the ages 40—60 years is

especially noteworthy. The decrease is here more pronounced among the women, amounting to 23 % as against 4 % among the men.

As may be seen from table 3, the decrease of cancer in the digestive organs in the ages 40—60 years is more marked than the decrease in the total cancer-mortality. In the ages 60—80 years the mortality is practically the same for the two periods. This is the more curious as cancers in the digestive organs comprise almost exclusively internal cancers that are difficult to diagnose.

Table 3 shows in all the age-groups a slight increase of cancer in the female genital organs. Unfortunately, the older statistics do not allow of any sub-division into mammary and uterus-ovarian cancers. As has already been mentioned, there are grounds for assuming that these two cancer-groups occur under different conditions, and this diminishes the value of an investigation of the frequency of the total female genital cancer.

The enquiry has shown that there is no increase in cancer-mortality in the ages under 60 years. Just as clear, however, does it seem that there is an increase in the ages over 60 years. As regards the ages over 80 years, the material for the period 1871—90 is so slight that it does not permit of any sure comparison. Among the men we find only 19 cases of cancer in this group during the twenty-year period. I have therefore made one group of the ages over 60 years. Table 2 shows in this group an increase of 45 % for the men and 15 % for the women.

There is reason to suppose that there is no actual increase in cancer-mortality in the ages over 60 years. The infirm aged in Stockholm are now cared for to a great extent in Old People's Homes and infirmaries with good opportunities for medical attention. They are, moreover, often sent there only after their diseases have been ascertained and diagnosed in a modern hospital with up-to-date equipment. The development that has taken place along these lines since the 1870's can without exaggeration be designated as revolutionary.

If one considers how much oftener senile debility (*marasmus senilis*) was adduced as the cause of death during the earlier period, one cannot but see herein a direct proof of how the diagnosis of the diseases of old people had advanced.

Table 6.

Annual mortality in Stockholm per 10,000 inhabitants from senile debility (marasmus senilis.)

Age group	Men		Women	
	1871—90	1934—38	1871—90	1934—38
60—80 years	44.7	6.5	47.7	7.9
over 80 " 	1,046.4	136.1	961.7	243.0

In comparison with the marked decrease in the diagnosis of death from senile debility the increase in cancer mortality in the higher ages is but modest. In the ages from 60 to 80 years the diagnosis of death from marasmus senilis has diminished 25 more than cancer mortality has increased. Such a comparison makes it difficult to conceive of any actual increase in cancer mortality in the higher ages. Even if the term senile debility may give rise to the suspicion of undiagnosed cancer, the increase in the figures for cancer mortality is thus in itself insufficient to explain the diminished role played by senile debility as a cause of death. Vascular diseases have taken over the role formerly played by senile debility as the dominating cause of death in old people. From 1871 to 1890 senile debility constituted, for ages above 80 years, one half of the diagnosis of cause of death and vascular diseases only about one tenth. During the period 1934—38, on the other hand, the reverse was the case.

Table 7.

Annual mortality per 100,000 inhabitants in certain causes of death in Sweden according to the Official Statistics.

Period	Unknown causes of death	Senile debility	Tumours
1911—1915	77.2	227.5	112.3
1916—1920	56.8	214.6	116.7
1921—1925	36.7	194.6	125.2
1926—1930	22.2	170.7	134.5
1931—1935	11.7	153.1	142.8
1936	4.7	145.6	154.0
1937	4.5	139.8	151.0
1938	3.8	129.5	151.7

In conclusion, it may be of interest to give some figures to illustrate the situation for the whole Swedish population. In table 7 are given figures representing the number of deaths per 10,000 inhabitants on account of tumours, senile debility and unknown causes.

These figures show that up to the present time the frequency of tumours as cause of death has increased, while Senile debility and unknown causes of death have diminished. As a matter of fact the increase in the frequency of tumours is much slighter than the decrease in the two other disease-groups. This may be due to the fact that when the diagnoses become more sure, unknown causes of death are distributed among not only tumours but also among other more definite causes of death. It is, further, of interest to consider figures from the Swedish rural districts, where in respect of the cause of death a distinction is drawn between proved and probable cause of death (Cf. table 8.)

Table 8.

Percentage distribution between »proved» and »probable» causes of death in country districts of Sweden in the groups tumours and senile debility according to the Official Statistics.

Period	Tumours		Senile debility	
	Proved	Probable	Proved	Probable
1911—1915	69.9	30.1	18.6	81.4
1916—1920	71.5	28.5	18.6	81.4
1921—1925	71.3	28.7	20.5	79.5
1926—1930	75.1	24.9	25.9	74.1
1931—1935	81.2	18.8	35.0	65.0
1936	83.8	16.2	40.6	59.4
1937	85.2	14.8	42.9	57.1
1938	84.3	15.7	42.9	57.1

Deaths in the country districts are of course not always diagnosed by physicians, but the data concerning cause of death are controlled by medical officials, who state whether the diagnosis is to be regarded as »proved» or only as »probable». (As has previously been mentioned, all causes of death in the urban districts are controlled by medical practitioners.) It emerges from the figures that the percentage of proved deaths caused by tumours rises considerably up

to the present time, and the percentage of cases with only probable diagnosis diminishes. As regards senile debility the development is the same. The percentage of demonstrable cases increases and the percentage of only probable cases decreases. The figures give a definite impression that the data have become increasingly reliable right up to the present.

Table 9.

Annual mortality per 100,000 inhabitants in various age-groups in cancer and senile debility.

Period	Cancer, age-group					Senile debility
	0—40	40—50	50—60	60—70	70—∞	
1911—1915						227.5
1916—1920	5.0	89.3	240.9	494.2	691.3	214.6
1921—1925	5.0	83.6	242.9	516.6	774.6	194.6
1926—1930	5.1	84.9	228.0	515.6	854.7	170.7
1931—1935	5.8	81.4	223.5	510.9	906.9	153.1
1936	6.2	88.8	220.4	527.5	980.2	145.6
1937	6.7	79.3	233.6	497.6	957.6	139.8
1938	6.3	81.8	215.8	489.0	971.4	129.5

Against this background it is now of interest to investigate the cancer-mortality in different age-groups. We find (cf. table 9) that mortality is fairly constant or has possibly diminished slightly up to the present time. The slight decrease is possibly connected with the fact that to a certain extent cases of disease could be treated successfully, so that the patient was restored to health and later died of some other disease, or in any case so that the death was postponed. This does not, however, hold good for the highest age-group over 70 years. For this group we get a strong increase, which, as appears from the table, should be seen against the background of a decrease in the mortality from senile debility. The figure should, probably simply be taken to imply that for the highest age-group increased diagnostic possibilities obtained, which resulted in the number of deaths from senile debility diminishing at the same time as the diagnosed cancer-mortality increased.

The figures for the whole of Sweden thus lend no support for the assumption that any considerable increase in the risk of dying of cancer has taken place.

Summary.

This study aims to contribute to the discussion whether there is an actual increase in the cancer frequency. The author maintains, that the solution of this problem lies mainly in mortality statistics. Several phases of cancer statistics are discussed in a review of the literature. The importance of age grouping of the materials is emphasized. Statistics of cancer mortality from districts with well analysed causes of death supports the assumption, that no actual increase in the cancerfrequency exists.

The authors own investigation is an inquiry into the cancer mortality in Stockholm during the last seventy years. It is shown that the official statistics of this city is a valuable source for the study of cancer frequency. The present study of the figures of Stockholm supports the opinion, that there is no actual increase in cancer frequency. Finally the author gives figures to illustrate the cancer mortality throughout Sweden. The result of this review agrees with the previous conclusion.

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Treatment of subacute bacterial endocarditis (endocarditis lenta) with heparin.

By

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Since the introduction of sulfanilamide and its derivatives in the treatment of bacterial infections it has been extensively used in various countries in the attempts to find a cure for subacute bacterial endocarditis (endocarditis lenta). The subject has been treated in some detail in monographs by Long and Bliss (1) and by Domagk and Hegler (2). The results achieved, however, have been relatively discouraging. One of the reasons for the many failures was thought to lie in the fact that the bacteria in the secondary nidus on the valves of the heart could not be affected by antibacterial substances circulating in the blood. The reason for this, in its turn, was to be sought in the structure of these secondary foci.

The generally accepted view is that the deposits on the valves are thrombotic in origin and that they have arisen from the deposition of fibrin and platelets by the blood circulating in the cardiac chambers. They are composed of an outer layer of fibrin and thrombocytes, an under layer rich in bacterial vegetations, and finally, underlying this, a fairly wide zone of necrotic tissue and fibrin. This lowermost layer merges, in its turn, into the more or less changed valvular tissue. Owing to the fact that the outer layer composed of thrombocytes and fibrin constantly increases in thickness, the bacterial vegetations are probably always protected from the influence of bactericidal agents in the blood stream, and

the bacteria are continuously being supplied with a new substratum for continued vegetation.

It was on the basis of this theory that Kelson and White (3), and Friedman, Hamburger, and Katz (4), began using heparin in the treatment of subacute bacterial endocarditis. The following passage is cited from the paper¹ submitted by the first-mentioned workers. »By present means it appears impossible to increase the number of phagocytes and draw them into contact with the bacteria, to dissolve the vegetations or to induce granulation within them. One can attempt, however, to prevent further thrombotic deposition on their surface in order to (1) restrict the nidus and culture medium for bacterial growth, (2) prevent embolism from the freeing of fresh thrombus, and (3) check the growth of the vegetations so that proliferating fibroblasts may fill in the areas thus limited.»

In the afore-mentioned work by Kelson and White, seven cases are mentioned and in three the results were favourable — in two the process had healed and in the third there were still no symptoms after a four-weeks' observation period. Kelson and White administered heparin by continuous intravenous drip for 14 days, and the heparin dose was regulated so as to make the clotting time five times the normal. Sulfapyridine was given before, during, and after the heparinization.

As the treatment suggested by Kelson and White seemed theoretically reasonable, and as the preliminary reports were relatively favourable, the heparin-sulfapyridine method was taken up with much interest by other workers and became the subject of further experiments. It was even recommended in an editorial in J. A. M. A. (116: 1646, 1941) (5).

Lichtman and Bierman (6) have published an excellent review of the treatment results in endocarditis lenta. They found that spontaneous healing occurred in 6 out of 634 cases, i. e. 1 per cent. With chemotherapy alone (sulfanilamide and its derivatives) healing occurred in 12 out of 198 cases, i. e. 6. per cent. When chemotherapy was applied in conjunction with heparin, or with hyperthermia or fever treatment, the number of cases treated was small. The number cured was relatively large, however. With the chemotherapy and heparin combination 5 cases recovered out of 43 treated, i. e. 12

¹ »A new method of treatment of subacute bacterial endocarditis using sulfapyridine and heparin in combination: preliminary report«.

per cent; with chemotherapy and elevation of the body temperature (by the application of warmth or by the injection of typhopara-typhoid vaccine) 9 out of 46 cases were cured, i. e. 20 per cent. Thus, in these small series, the combined methods yielded better results than chemotherapy alone; the combination of a raised body temperature and chemotherapy seemed especially promising.

As regards the value of the heparin and chemotherapy combination, certain doubts have arisen as time has gone on. Friedman (7), who was one of the first to suggest this combination, now considers that heparin, either alone or in the mentioned combination, is not effective in the treatment of subacute bacterial endocarditis. Leach, Faulkner, Duncan, McGinn, Porter, and White (8) reported that, of 18 cases which had chemotherapy alone, 1 was cured, and of 17 which received chemotherapy as well as heparin, 3 were cured. They summarized their findings as follows: »Sulfapyridine and perhaps sulfathiazole are useful drugs in the treatment of subacute bacterial endocarditis. Heparin has not alone been effective in the treatment of the disease, but it may have acted as a favorable adjunct in some of the cases in which recovery occurred (3 out of 4).» In a note appended to the paper cited, Kelson (8) remarked that the prospect of succeeding with the combined heparin and sulfapyridine treatment is wholly dependent upon whether or not the infection can be influenced by sulfapyridine. If it can not, then the heparinization has no effect. McLean, Meyer and Griffith (9) also expressed doubts as to the usefulness of heparin in the treatment of endocarditis lenta.

Three clear-cut cases of subacute bacterial endocarditis of the lenta type have been treated during 1941 and 1942 at the medical clinic at Karolinska Sjukhuset, in accordance with the principles followed by Kelson and White. A report of the cases is appended further on in this communication.

At the postmortem examination performed on one of these patients (no. 3) a fresh deposit of red thrombus on the valves was observed. The heparinization had obviously not succeeded in preventing the continued deposition of thrombotic material on the valves. Thus, the basic condition for a successful therapeutic result was not fulfilled according to the theory underlying Kelson and White's heparin treatment. Heparin is the physiologic anticoagulant agent, but whether it prevents a precipitation of fibrin on in-

flammatory tissue is perhaps open to doubt, at least with doses of the size given in the cases to be reported.

Fletcher (10) asserted that, if the reasoning upon which the treatment of Kelson and White is based is really correct, then heparin alone ought to be effective in dealing with subacute bacterial endocarditis, without a concurrent administration of sulfanilamide derivatives. In this author's opinion, the antibacterial defences inherent in the organism itself ought to be capable of overcoming the *Streptococcus viridans*, which is of no great virulence, and if the continued deposition of fibrin and platelets on the valves could be stopped the infecting foci would be sterilized by the organizing connective tissue. Working on this assumption, he tried heparin alone in a case of endocarditis caused by *Str. viridans*. The heparin was administered for 14 days by intravenous drip on the Kelson and White principle, and the clotting time was kept at or above four times its normal value. The patient died of cerebral hemorrhage while the treatment was in progress. At autopsy it was found that the deposits on the valves were essentially the same as those observed in untreated cases, and that recent deposition of fibrin had taken place. Fletcher stated: »It may be concluded that heparin treatment of subacute bacterial endocarditis is both dangerous and ineffective.»

The observations made in regard to the cases to be reported from Karolinska Sjukhuset tallied in the main with those of Fletcher. Thus, in these cases of endocarditis, heparin could not prevent the deposition of fresh thrombotic material on the valves of the heart. The postulate that the disease can be favourably influenced by heparin therefore did not apply.

It may be mentioned that the view that the deposits on the valves are composed mainly of thrombi thrown off by the blood passing through the heart chambers is not held by all workers. Allen (12), for instance, considers that the majority of the »deposits» are probably derived from the valve itself — that they are proliferating and necrosing fibroblasts and other valvular tissue. He mentions that normal valves are poorly vascularized, but that in patients who have had rheumatic endocarditis the valves contain capillaries. In subacute bacterial endocarditis these vessels might deliver blood constituents in the valve. It is also possible that a new formation of blood vessels takes place during the course of a subacute bacterial endocarditis just as it does in all other inflammatory processes.

Case 1. I. S. A., a married woman of 25. Stay in hospital, June 27, 1940, to July 15, 1941, and Nov. 19 to Dec. 1, 1941.

This was a typical case of subacute bacterial endocarditis of the septic type. The patient had a combined lesion of the aortic and mitral valves as a result of rheumatic polyarthritis at the age of 9 years. There were no signs of cardiac incompensation. About 14 days before her admission to the hospital her temperature rose to between 39°C and 40°C without local symptoms. A blood culture was positive for alpha hemolytic streptococci. This patient lived for about one and one-half years after the appearance of the bacterial endocarditis symptoms. She was cared for at the clinic for a little over a year, then at home for a few months, and she was finally re-hospitalized a week before her death.

She was given various sulfanilamide derivatives, the best effect being achieved with sulfapyridine. This preparation was administered for about 9 months, in a dose of 7 g a day, which gave a blood level of 13—14 mg per hundred cubic centimeters (free = total). No signs whatever of granulocytopenia were observed. It was possible to keep the temperature subfebrile, or afebrile, but blood cultures still yielded growths of alpha hemolytic streptococci. Concurrently with this treatment, a dose of 75 mg of heparin was administered 4 times a day for 22 days through an Olovson (13) needle. At this stage the patient weighed about 45 Kg. No determination of the clotting time was done. No effect from the heparin treatment was noted.

In this case, the course of the disease could not be checked even though very large doses of sulfapyridine were given for an uncommonly long period; nor did the heparin treatment have any noticeable effect. The patient finally died of the after-effects of cerebral embolism. The emboli did not develop, however, until long after the close of the heparin treatment, and had no connection with it. (The case is reported in detail in *Nordisk Medicin* 14: 1834, 1942.)

As regards the heparin dosage in this case, as in the two following cases, the principle followed was that agreed upon at the Annual Meeting of the Swedish Society for Internal Medicine in 1940 (11).

Case 2. K. E. B., a married woman aged 27. Stay in hospital, Jan. 23 to Apr. 7, 1941.

This was a well-defined case of fairly far-advanced subacute bacterial endocarditis of the septic type. The patient already had a chronic valvular disease — aortic regurgitation, — but she was not decompensated. She contracted fever without local symptoms about 7 months before her admission to Karolinska Sjukhuset. She had been treated at another hospital, however, for 5 months before being admitted to our clinic, and during that time she had had high fever, with a temperature ranging between 38°C and 39°C . A blood culture contained growths of alpha hemolytic streptococci. On her admission, her temperature was 39.1°C and there were signs of lesions of the aortic and mitral valves. She was emaciated and weighed 37 Kg. After receiving sulfapyridine (1 g \times 6) she became afebrile, but 5 days later a toxic exanthem, with a rise in temperature reaching 39°C , ap-

peared. The blood levels were 13.2 mg per hundred cubic centimeters of free, and 15.9 mg per hundred of total, sylfapyridine. The sulfapyridine medication was continued despite the exanthem but the temperature did not subsequently fall below 38° C. After a negative blood culture had been obtained, heparin therapy was started in accordance with the Kelson and White system — 75 mg of heparin were given 4 times a day through an Olovson needle, and this heparinization was continued for 14 days. The clotting time was not determined. After 11 days granulocytopenia developed, the lowest white blood count being 2,000 per mm³. The sulfapyridine treatment was broken off but the heparin was continued for a further 3 days. No effect from the heparin was apparent. The patient overcame the leukopenia and about 14 days later leukocytosis was present (22,000 whites per mm³). Growths of alpha hemolytic streptococci were still present in the blood cultures. Another attempt with heparin was now made, 75 mg being given intravenously 4 times a day through an Olovson needle for 31 days. The temperature was still in the neighbourhood of 38° C. During the heparinization the patient expired, the immediate cause of death being a subdural hematoma. At autopsy large friable deposits of the aortic valves were seen, two of them showing perforation. The deposits on the posterior aortic valve encroached upon the anterior mitral valve. (A detailed report of the case appeared in *Nordisk Medicin* 14: 1834, 1942.)

Case 3. A. L. S., a female clerk aged 18. Stay in hospital, Jan. 9 to Mar. 2, 1942.

A typical case of subacute bacterial endocarditis. She had had a chronic valvular disease — combined lesions of the aortic and mitral valves — since the age of 12, when she had rheumatic endocarditis, but there were no signs of cardiac insufficiency. Just before her admission to the clinic the patient had given birth to a child (Dec. 19, 1941). Her pregnancy and delivery had been normal. The subacute bacterial endocarditis had probably started some time at the beginning of December 1941, in connection with an acute infection in the upper respiratory tract with nasal catarrh, a temperature of about 40° C, and an ache in the left hip lasting a few days. Sulfathiazole was prescribed and the patient took about 50 g before her admission. She was afebrile as long as she was taking the tablets but the temperature rose as soon as she discontinued them. On her arrival at the obstetric clinic (Dec. 19, 1941) her temperature was 37.6° C. She was delivered the same day. Her temperature subsequently varied between 38° C and 39° C, and during the week before her admission to the medical clinic it was between 37° C and 38° C. She had received 1 g of sulfathiazole 5 times a day, but on account of a suspected toxic exanthem the drug was withdrawn just before her transference to our clinic.

When admitted to the medical clinic the patient was in good condition and showed no clinical signs of failing cardiac function. From the heart there were indications of a combined valvular disease (stenosis and insufficiency of the mitral and aortic valves). Just before and after her admission blood cultures yielded abundant growths of alpha hemolytic streptococci.

The patient was treated at the clinic for a little more than 7 weeks before she died. The temperature was continuously febrile; for the first 14 days it varied between 39° C and 40° C, and subsequently between 38° C and 39° C. Three days after she arrived, when the diagnosis had been fully confirmed, treatment with heparin and sulfapyridine, or sulfathiazole, was begun. The amount of the sulfanilamide derivative varied, but the blood level was generally maintained at 6—12 mg of free sulfapyridine or sulfathiazole per hundred cubic centimeters. To begin with, the heparin dose was 75 mg 4 times a day. (The patient weighed 52 Kg, and calculated on an amount of 1.5 mg of heparin per Kg of body weight she should have received 78 mg 4 times a day.) After 11 days the daily heparin dose was increased to 55 mg 6 times, and after a further 3 days to 60 mg 6 times a day. This latter dose was continued for 35 days (until the patient's death). Thus, heparin was given for 49 days. It was administered for 5 weeks through an Olovson needle, and for the remaining period by intravenous drip. On account of nausea and vomiting, for the last 12 days an intravenous drip had to be set up and the chemotherapeutic agents and heparin injected through the tube. During practically the whole period there was leukocytosis, the white cell count being between 10,000 and 20,000 per mm³. With the aid of blood transfusions (to which heparin was added) the hemoglobin content was maintained at about 70 per cent and the number of red blood cells at about 3,500,000 per mm³. After 52 days' treatment the patient expired, exhibiting the picture of a cerebral hemorrhage which had developed within a few hours.

The following passages are cited from the postmortem examination (performed by Docent Ringertz).

»Aortic valves: Marginal fibrosis, and an old, healed lesion were present. At one area, roughness and tough, flaky deposits. On the anterior valve, a tough polypus the size of a brown bean, with a fresh (red) thrombus on its cupola. Mitral valves: On the anterior valve, a polypus similar to that on the aortic valve. There was also rough scarring on the posterior valve and on the posterior wall of the left auricle covering an area the size of a 5 öre piece. The aortic ostium was narrowed to less than two fingers' breadth; a certain insufficiency seemed in question here. The mitral orifice would not admit two fingers. Microscopically, the valves of the heart presented the picture of an ulcerous thrombo-endocarditis. In places there were only old lesions showing vascularization and fibroblastic proliferation. In most of the areas examined, however, an acute thrombo-ulcerous process, with plentiful leukocytic infiltration and bacterial foci in the thrombi, was superimposed on these old lesions.

Autopsy of the brain revealed under the dura on the left side a blood clot containing about 100 cm³ of blood, and concentrated around a walnut-sized focus at the left occipital pole. A number of small, massive hemorrhages were present in the cortex and in the subcortical white matter.»

Thus, in this case, a fresh red thrombus was formed on the valves during the heparin treatment. The heparin doses were comparatively large — towards the end of the treatment, 360 mg per day for a person weighing about 50 Kg.

Summary.

A report is made of three cases of subacute bacterial endocarditis (endocarditis lenta). The patients were treated with sulfapyridine and heparin. The heparin proved to be ineffective in these cases — the clot formation was not prevented.

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Heparin treatment in cardiac insufficiency with intermittent auricular fibrillation and multiple embolism.

By

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Since the chemical nature of heparin was cleared up by Jorpes and a sufficiently pure preparation was made available on the market, it has been extensively used in the treatment of thrombosis, both as a prophylactic and as a curative for already existing thrombosis in the vessels forming the sources of the iliac and femoral veins (Crafoord, Wetterdal, Bauer, Hellsten). As far as the specific internal diseases are concerned, the use of heparin is still fairly limited. Nevertheless, favourable results have been reported, in a few instances, regarding the treatment of thrombosis in the posterior inferior cerebellar artery, the Wallenberg syndrome (Magnusson). Heparin is at present also being tested as a therapeutic in coronary occlusion; no definite statements as to its effectiveness in this difficult field have as yet been made, however.

At the medical clinic at Karolinska Sjukhuset, we have tried heparin treatment on a few patients suffering from cardiac insufficiency with intermittent auricular fibrillation and emboli in various parts of the body, and as far as could be judged the results were satisfactory.

During periods of auricular fibrillation, which are often manifestations of intensified cardiac insufficiency with dilatation of the

auricles, thrombi sometimes form in the auricles. It is well known that the risk of embolism resulting from thrombi thus formed not seldom exists if the heart begins to contract with greater force, as it does, for instance, under digitalization. If thrombus formation could be prevented, in insufficiency of the mitral valve with auricular fibrillation to take an example, the attacks of embolism might be forestalled. Clot formations might possibly be prevented by heparinization of the patient. It is of course not certain, or even probable, that any permanent improvement can result from this measure, since heparin cannot be administered indefinitely. We have made an attempt with two patients, however, and have achieved good results, at least as regards the case in which the observation time has been fairly long. The reason why the improvement has been lasting cannot be stated with certainty.

Case reports.

Case 1. (No. 152/1940). M. E. K. N., a widow aged 54 years was admitted to the medical clinic under the diagnosis cardiac infarction, which subsequently proved to be correct. During her stay in hospital she suffered from intermittent auricular fibrillation and repeated attacks of pulmonary embolism. On account of these attacks which, as already mentioned, might have been causally connected with the fluctuations in the heart rhythm, she was heparinized for a certain time. In direct connection with this treatment a striking change for the better occurred — there were no further attacks of pulmonary embolism, the heart beat became regular, and the patient was discharged as well as she had been before the start of her illness. After a two-year observation period she is still in good health, has managed her own household, taken daily walks, and not suffered especially from shortness of breath. She has had isolated attacks of auricular fibrillation and precordial pain. It is the noticeable improvement occurring in connection with the heparin treatment that has led to the publishing of the case.

Case history. The patient was born in 1886. Her previous history contained nothing relevant until 1920, when she had clots in both legs after an attack of typhoid fever. Since then she had occasionally felt as if her heart «skipped a beat», particularly when the abdomen had been distended with gas; possibly also, she had been shorter of breath than before. For about 14 days in 1924 or 1925 she had had an ache and swelling in the right knee and a temperature of about 38 C. The physician called in diagnosed the condition as rheumatic fever. In 1938 she had a return of the discomfort in the right knee and spent some time at the surgical clinic. Tuberculosis was suspected, but a specimen taken did not confirm this. In the summer of 1939 her hands and wrists ached and swelled.

In the summer of 1939 also, a sudden nocturnal attack of uneasiness, palpitation, and irregular action of the heart, lasting two hours. No further attacks until February 1940, when she had another one similar to the last. She was hospitalized under the diagnosis chronic valvular disease and paroxysmal tachycardia. On auscultation the cardiac rhythm was regular, and a blowing systolic murmur, audible over the entire heart, was soft over the apex and harsh at the aortic area. The blood pressure was 210/110. At a roentgen examination the heart showed regular pulsations. The heart measured 12.5 cm in length, 10 cm in width, and 9 cm in depth, and was normal in size and shape. The heart volume was 480 cm^3 — 280 cm^3 per square metre of body surface. The hili of the lungs, the pulmonary parenchyma, and the pleurae presented no roentgenographic abnormalities. The patient was discharged after a week's observation and put on 0.1 g of quinidine sulfate twice a day.

She had no further heart trouble until Aug. 29, 1940, when she had fresh attacks of cardiac irregularity, fever, and general malaise; she found it difficult to take deep breaths. The following day (Aug. 30), another attack of heart trouble and precordial pain, and one day later (Aug. 31) still another, with pains around the heart and irregular rhythm. On Sept. 2, after an attack of unusually severe pain, she was hospitalized.

Physical examination. (Sept. 3, 1940) No pain since her admission. Her general condition was unaffected and there were no definite signs of incompensation. The heart rate was rapid, and regular for the most part, with an occasional, quick auricular fibrillation. Over the third left intercostal space, adjoining the sternum, was heard a murmur which was difficult to localize as to time but which was possibly a pericardial friction rub. Blood pressure, 150/100. Leukocyte count, 10,300 per mm^3 . Sedimentation rate, 75 mm in 1 hour. Temperature, 37.9 C. An electrocardiogram taken the same day showed the rhythm to be regular. Heart rate, 120 beats per minute. A—V conduction time 0.15 sec., and Q—S time 0.08 sec. The ventricular complexes showed normal tracings. The S—T segment was also normal. Roentgenograms of the heart and lungs taken on Sept. 7 yielded the following information. Heart volume, 360 cm^3 per square metre of body surface. No abnormality in the shape or size of the heart. The aorta was fairly long but displayed no local dilatation. No stasis or other pathologic changes apparent in the lungs. In the left pleura there was a minimal quantity of free fluid. At auscultation a systolic murmur, loudest over the third left intercostal space and close to the sternum, was heard after the heart rate had somewhat subsided. In all probability it was a question of cardiac infarction, although electrocardiographic changes were not yet evident.

The patient was treated with theophylline and Pandigal (a *Digitalis lanata* preparation), and for the next six weeks her condition was fairly satisfactory. She had occasional attacks of auricular fibrillation, and the blood pressure remained at about 145/100. Her temperature bordered on subfebrile. On Oct. 13 the temperature rose and pains were experienced in the left thorax on deep inspiration. A roentgen examination revealed a

parenchymal area of density at the base of the lungs. Auscultation yielded nothing new from the heart or lungs. An electrocardiogram now showed depression of the S—T segment which might well have been due to the digitalis effect. The elevation in temperature lasted for about a week, the highest level being 38.8 C. Some days after the appearance of the pains, dullness and weakened respiratory sounds were heard basally over the left lung. The temperature again became subfebrile. Occasional attacks of auricular fibrillation occurred and a murmur, which was interpreted as a pericardial friction rub, was heard. There were still no electrocardiographic signs of infarction. This was probably the first attack of pulmonary embolism.

About a week after the temperature had returned to normal, it rose again to over 39 C, and she experienced a stabbing pain in the right side (Nov. 1). The white cell count was about 15,000. A physical examination of the lungs now produced no signs of a pulmonal or pleural process. A couple of days later the patient complained of smarting pain behind the sternum and of a sensation of heaviness on inspiration. The pericardial friction rub was still audible over the heart. The cardiac rhythm was regular. The temperature varied between 38 C and 39 C and remained at this level for about 4 weeks. An electrocardiogram taken on the first day of this fever period showed no variations from the previous tracings. On the other hand, an electrocardiogram taken on Nov. 4, i. e. 1 week after the beginning of the latest elevation in temperature, showed signs of auricular fibrillation, and among ventricular complexes of normal appearance there were some of a divergent type, which were thought to be due to intermittent bundle-branch block. The heart rate was 120—160 beats per minute. The S—T segments were changed, but the nature of the change could not be determined. Another electrocardiogram taken two days later still showed evidence of intermittent bundle-branch block and auricular fibrillation; the tracings were otherwise of the type seen in left ventricular preponderance with signs of left-sided myocardial damage. On Nov. 7, weakened respiratory sounds over the base of the right lung, a large harsh râle, and a pleural friction sound. She felt a stabbing pain in the right side of the thorax. At this stage she was rather poorly. She had a stitch, was short of breath, and edematous on both forearms, over the sacral region, and in both legs. As bronchopneumonia was strongly suspected sulphyridine was given, at times by intravenous injection on account of nausea, which precluded medication by the mouth. The electrocardiogram was unchanged. There was an intermittent auricular fibrillation. The discomfort slowly receded and her condition improved.

It is difficult to know what was the reason for this long period of fever and illness. In the author's opinion, a fresh coronary occlusion (the electrocardiographic changes which later persisted), and pulmonary embolism on the right side (the pleural friction sound and the other lung findings) is the most probable explanation.

At the beginning of December the temperature was afebrile. The legs was the same as before. She was still faintly edematous in the lower extremities.

and had a slight stitch and a friction sound over the right lung flank. No friction rub over the heart. The rhythm was regular. In the middle of December, a new rise in temperature, of relatively short duration, and a simultaneous auricular fibrillation attack; then a rather long, afebrile period until the beginning of January 1941, when a slight temperature rise accompanied by a stitch in the left thorax and pleural friction sounds occurred. These symptoms persisted for a fairly long period but finally, at the end of January, the temperature became afebrile again. On a roentgenogram it was seen that the heart measured about 14 cm in length, 10.5 cm in width, and 8.5 cm sagittally. The heart volume was about 525 cm³. A small pleural exudate which, when the patient lay on her left side, shifted out along the thoracic wall, was visualized in the left thorax. The lungs and heart otherwise presented a roentgen picture similar to that already obtained.

The findings were compatible with a fresh attack of pulmonary embolism on the left side.

At the beginning of February 1941, another elevation in temperature reaching over 38 C. and lasting just about a fortnight. There was now a pleural friction rub over the right lung base. Probably another attack of pulmonary embolism, this time to the right.

An electrocardiogram taken on Feb. 3 now clearly indicated right-sided bundle-branch block in all ventricular complexes. (This heart block, and otherwise unaltered tracings, were present on all subsequent electrocardiograms, the last of which was taken on Apr. 25, 1942.)

After an afebrile period lasting about 3 weeks another arrhythmic period with a temperature rise and a right-sided pleural friction rub set in during the first days of March. A probable pulmonary embolism to the right.

On Mar. 11, a further rise in temperature, uneasiness, precordial pain, and a chafing sensation in the left thorax. The blood pressure was about 90 mm. (It was, as a rule, 120—130 mm at this stage.) After stimulation she was better. Pulmonary embolism to the left was the probable cause of the trouble.

On Mar. 12, the following entry was made in the records: »The patient's repeated attacks of pleural irritation (friction rubs and stabbing pains), of varying location, are presumed to be due to pulmonary emboli. Their origin is unknown, but it is believed to be the right auricle. It is thought likely that the emboli are thrown out during the alternation between the auricular fibrillation and the regular heart rhythm. On the basis of this supposition heparin treatment is tentatively started.» The patient received 75 mg 4 times a day through an Olovson needle. This heparinization proved satisfactory. The blood pressure showed a slight tendency to fall in connection with the injections but this could be avoided by a slow rate of injection. The temperature fell rapidly to afebrile, there were no further subjective or objective signs of pleural irritation (pulmonary embolism), and no attacks of auricular fibrillation. The heparinization was discontinued after 3 weeks. By that time the patient's general condition was excellent, and she could sit up. She was discharged on Apr. 10.

During almost the entire period she was given Pandigal (a *Digitalis lanata* preparation), theophylline, and phenobarbital. For 11 days at the beginning of December (Dec. 7—18) she took 0.1 g of quinidine sulfate 3 times a day.

Since being discharged she has been on digitalis, quinidine, and theophylline. Her ankles sometimes swell towards evening, and she has had occasional short attacks of auricular fibrillation and precordial pain. The latter were the cause of a short stay at the clinic in April 1942. No marked change of the status was noted. A roentgenographic examination showed that the shape and size of the heart had not changed since the preceding examinations. The pleural area of density at the base of the left pulmonary field had completely disappeared. No fresh changes were apparent in the pulmonary fields.

Case 2. (No. 427/42.) E. M. J., a married woman aged 57 years, had been treated at the clinic about 8 months earlier on a diagnosis of chronic myocarditis, marantic thrombosis, and thrombosis of the left leg. She had first been admitted to the surgical clinic on a suspicion of appendicitis but because of her low state of health the operation had not been performed. Immediately prior to her admission she had suddenly become ill from epigastric pains which radiated toward the right iliac fossa and out into the back. A dull ache in the abdomen alternated with the pains. She was tender over McBurney's point, and leukocytosis was present. The pains gradually disappeared but the temperature remained subfebrile. During her stay at the surgical clinic a blood pressure of 230/100 mm Hg was measured. She had had heart trouble for several years in the form of occasional rapid uneven beating. While at the surgical clinic left hemiplegia developed without causing disturbance of the speech faculty. An electrocardiogram showed faint signs of myocardial damage in the form of small depressions of the S—T interval. On examination at the medical clinic reduced muscular power in the left arm and leg were noted. The electrocardiographic tracings now plainly showed depression of the S—T intervals. After a few days' observation she was referred to a nursing home.

In view of the subsequent course, it is possible that the previously mentioned abdominal pains were caused by mesenteric embolism, and that the symptoms from the cerebral nervous system were due to cerebral embolism.

Her health gradually improved to such an extent that she was able to get up. Her legs usually swelled in the evening, particularly the left leg, which she was obliged to bandage.

The patient was re-admitted to the medical clinic on Mar. 16, 1942. A couple of weeks before this she had begun to cough, and had produced about a coffee cup of blood-streaked sputum a day. On Mar. 13 she suddenly experienced intense pains in the lower part of the thorax, under the costal arch, occurring at every breath and at every movement. Her body temperature was over 38 C. After the appearance of the pains she had no further

On admission her temperature was 39.1 C and the white blood count 12,600 per mm³. Sedimentation rate, 47. She was slightly dyspneic and rather pale, but not cyanotic. There was no edema. Physical examination of the lungs yielded dullness, weakened respiratory sounds, and a pleural friction rub at the right base. Over the heart was heard a distinct, harsh systolic murmur, loudest at the apex, and a rapid auricular fibrillation. Blood pressure, 125/80. A roentgenogram of the lungs showed dorsally, in the basal part of the right pulmonary field, a fairly massive, diffuse, wedge-shaped shadow its apex pointing towards the hilum of the lung. The right posterior sinus was not visible and the right diaphragm was elevated. As the picture seemed indicative of bronchopneumonia, sulfapyridine treatment, followed by sulfathiazole, was begun. On account of the auricular fibrillation and pulse deficit digitalis was given. The temperature remained at 38 C or 39 C for over a week. Sedimentation rate, 102. After this, she was subfebrile and the sulfanilamide derivatives were discontinued. At a roentgen examination of the lungs, after she had been subfebrile for somewhat less than a week, it was found that the shadows at the base of the right lung field had decreased. The pleural area of density had increased and was now seen to be encroaching on the pulmonary field in a convex bulge from the back. An encysted exudate was probably in question. The sedimentation rate at this stage was 106. The records contain no mention of when regulation of the heart rhythm occurred. An electrocardiogram taken on Apr. 8 showed a regular rhythm, and a myocardial damage was evidenced by moderate depression of the S-T intervals. Temperature still subfebrile. Sedimentation rate, 37.

On Apr. 9 she had sudden severe pain in the abdomen, over which there was marked tenderness, most intense in the right iliac fossa. There was no true resistance, and no spontaneous escape of gas. The surgeon consulted considered that the picture chiefly resembled thrombosis of the mesenteric vessels (emboli?). There was no elevation in temperature. Heparin was administered in small doses (100 mg \times 2) for 3 days, and the patient improved subjectively. Sedimentation rate on Apr. 16, 44. A roentgenogram of the lungs on Apr. 21 yielded approximately the same picture as before. The temperature was subfebrile. On May 12, the following entry was made in the records: »The patient is suffering from abdominal pains similar to those she had before. Abdominal tenderness has persisted and resistance has been noted in the right side of the abdomen. Occasional auricular fibrillation occurs.» The sedimentation rate was 14. On May 21, the lungs were roentgenographed, and the shadow visualized dorsally to the right was seen to have decreased a little. The temperature was still subfebrile and the sedimentation rate 12.

On May 25, fresh pains in the thorax and the region of the heart. The temperature rose to 38.9 C but fell again a couple of days later to subfebrile. Sedimentation rate on May 28, 26. As a new attack of thrombosis was suspected, 100 mg of heparin were given 4 times a day through an Olovson needle. The patient weighed about 38 Kg. On May 29, it was recorded that the

pains had disappeared and that the temperature was normal (? subfebrile). The heparin therapy was continued until June 3, i. e. for a total of 10 days. The sedimentation rate was 35. After the heparin was withdrawn the temperature fell slightly and 14 days later it was just bordering on subfebrile. No attacks of auricular fibrillation or fresh signs of embolism have been observed since then. The electrocardiogram taken on June 2 still resembled the earlier tracings.

The picture might be interpreted in the following manner.

The patient had had cardiosclerosis and an intermittent auricular fibrillation for some years. During the past year emboli appeared in various parts of her body — in the mesenteric vessels on repeated occasions during the previous and the present stay in hospital, and in the cerebrum and the lungs. There was possibly a causal connection between the attacks of embolism and the alternations in the heart beat — during the periods of auricular fibrillation a thrombus might have formed in the auricles and been thrown out into the blood circuit when the auricular contractions again occurred. On the basis of this reasoning, heparin treatment was instituted with a view to preventing the formation of new clots in the heart and thus possibly breaking an imaginary vicious circle. In this case there was no reason to suspect cardiac infarction. The heparinization of the patient had a successful outcome in this instance also; the observation time, however, is as yet too short to allow definite conclusions to be drawn.

Summary.

A report is made of two cases of cardiac insufficiency with intermittent auricular fibrillation and repeated attacks of embolism in various parts of the body. The patients were treated with heparin, digitalis, and purine derivatives. In both instances definite improvement resulted from the heparinization. No further emboli occurred, the patients were able to get up, and the attacks of auricular fibrillation became less frequent.

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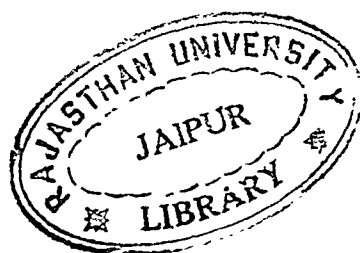
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